NDA 20451

NDA 20-451

AP Ltr
AE Ltr
Draft LBLG
CSO Rx. of LBLG
MOR
Stat
Bio

Pharm/Tox
Clin. Pharm/Bio
Chem
Micro
Memos

AP Ltr
AE Ltr
Draft LBL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 27 1995

NDA 20-451

QLT Phototherapeutics Inc.
Attention: Mr. Jonathan Kahan
Hogan & Hartson
555 Thirteenth Street, N.W.
Washington, D.C. 20004-1109

Dear Mr. Kahan:

Please refer to your April 12, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Photofrin (porfimer sodium) for Injection, 75 mg vial for use in photodynamic therapy with the following devices:

1. The OPTIGUIDE Fiber Optic Diffuser; and

2. the Coherent Lambda Plus PDL1 and PDL2 Photodynamic Lasers; or

3. the Laserscope Series 600 Dye Modules (Models 630 and 630XP) and the Series 700 and 800 KTP/532 or KTP/YAG Surgical Lasers.

We acknowledge receipt of your amendments dated December 4 and 13, 1995.

This new drug application provides for Photofrin for use in photodynamic therapy for palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with ND-YAG laser therapy.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated December 13, 1995 with the revisions listed below. Accordingly, the application is approved effective on the date of this letter. We note that the mock versions of the vial label and carton labeling have not been submitted. This approval does not preclude further revision of the final printed labeling, including the vial label and carton labeling. Please submit these mock versions as soon as possible. As discussed by telephone on December 19 and 20, 1995 between Alexandra

Mancini and Paul Zimmerman of this Division, the revisions to the draft labeling, as agreed, are as follows:

1. The drug name, as stated in the titie and first line of the DESCRIPTION section and on the first line of the HOW SUPPLIED section of the package insert, on the vial label and on the carton labeling, will be PHOTOFRIN® (porfimer sodium) for Injection.

2. In the DOSAGE AND ADMINISTRATION section, the sentence, "However, experience has indicated that mandatory debridement may not be necessary due to natural sloughing action in the esophagus and may, in fact, needlessly traumatize the area." will be changed to, "More recently, experienced investigators have indicated that mandatory debridement may not be necessary due to natural sloughing action in the esophagus, and may needlessly traumatize the area."

3. In the third line of Pharmacokinetics subsection of the CLINICAL PHARMACOLOGY section, the word "hour" will be changed to "hours".

Additional required changes are indicated on the attached marked-up labeling.

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

We remind you of your Phase 4 commitments specified in your submission dated December 4, 1995. These commitments, along with any completion dates agreed upon, are listed below. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

1. To design and perform a phase 4 single-arm study to assess the efficacy (dysphagia response) and safety of PHOTOFRIN-PDT in patients with partially obstructing esophageal cancer who, in the opinion of their physician, can not be satisfactorily treated with ND-YAG laser therapy. The specifics of the study design and patient population will be agreed upon with the Agency prior to finalization of the protocol. The limitation of recommended use of

PHOTOFRIN to patients with complete obstructions and partial obstructions only where ND-YAG laser cannot be used is based on safety concerns. There has not, however, been a trial carried out prospectively in the latter population to define effectiveness rates. We acknowledge your statement that a draft protocol, which may include the collection of pharmacokinetic data in patients as described in 2. below, will be provided to the Agency for comment in April, 1996;

2. to conduct phase 4 studies to gather further pharmacokinetic data in patients with hepatic impairment and in patients who have received more than one course of therapy. Pharmacokinetics will also be characterized in male and female patients. We acknowledge your statement that this will be completed by April, 1996;

3. to develop and validate the capillary electrophoresis (CE) assay, capable of fingerprinting the oligomeric mixture of PHOTOFRIN (porfimer sodium) for Injection, for product release and expiration dating. The Agency recognizes the complex nature of this drug product and acknowledges that full identification and characterization of all the components in the drug product may be difficult. However, the responsibility remains for you to adequately control and qualify the drug product. We acknowledge your statement that this will be completed by October, 1996;

4. to incorporate a standard in the routine HPLC assay, investigate the two wavelengths in the HPLC assay for detection of possible nonheme impurities, and validate a test for volatiles (acetic acid). We acknowledge your statement that these will be completed by May, 1996; and

5. to perform a validation study for the effectiveness of the sterile filtration process using PHOTOFRIN. We acknowledge your statement that a final validation report will be available in July, 1996.

Regarding our suggestions, transmitted in our July 13, 1995 approvable letter, to consider retesting the genotoxity of PHOTOFRIN and to consider characterizing the mass balance of PHOTOFRIN in humans to the extent possible, we acknowledge your statement that such tests will be considered in the continuing development plan for PHOTOFRIN.

Please submit fifteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-451. Approval of this labeling by FDA is not required before it is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Oncology Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Paul Zimmerman, Consumer Safety Officer, (301) 594-5775

Sincerely yours,

Robert Temple 12/26/95

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-451
HFD-150/Div. files
HFD-150/CSO/PZimmerman
HFD-2/M.Lumpkin
HFD-100 (with labeling)
HFA-100
HF-2/medwatch (with labeling)
HFD-80 (with labeling)
HFD-150/GWilliams
HFD-150/JRJohnson
HFD-150/AMurgo
HFD-150/YHsieh
HFD-150/CHoiberg
HFD-150/RJustice
HFD-150/JDeGeorge
HFD-150/DMcGuinn
HFD-150/RWood
HFD-426/MMehta
HFD-426/ARahman
HFD-713/SWilson
HFD-713/CGnecco
HFD-713/AKoutsoukos
HFZ-410/RFelten
HFD-150/DPease
HFD-160/PCooney
HFD-160/CVincent
HFD-643/NSager
DISTRICT OFFICE
HFD-240/S.Sherman (with draft labeling)
HFD-638 (with draft labeling)
drafted: PFZ/December 19, 1995/c:\wpfiles\20451.nda\letters\apletter
r/d Initials: YHsieh/12-20-95
RWood/12-21-95
JDeGeorge for DMcGuinn/12-20-95
JDeGeorge/12-20-95
AKoutsoukos/12-21-95
AKoutsoukos for CGnecco/12-21-95
ARahman/12-221-95
MMehta/12-21-95
GWilliams/12-20-95

JRJohnson/12-20-95
DPease/12-21-95
RDeLap/12-22-95

final type PZimmerman: 12-22-95 12/22/95

APPROVAL 12/26/95

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-451

JUL 13 1995

QLT Phototherapeutics Inc.
c/o Mr. Jonathan Kahan
Hogan & Hartson
555 Thirteenth Street, N.W.
Washington, D.C. 20004-1109

Attention: Mr. Jonathan Kahan

Dear Mr. Kahan:

Please refer to your April 12, 1994 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Photofrin (sterile porfimer sodium) for Injection, 75 mg vial for use in photodynamic therapy with the following devices:

1. The OPTIGUIDE Fiber Optic Diffuser; and

2. the Coherent Lambda Plus PDL1 and PDL2 Photodynamic Lasers; or

3. the Laserscope Series 600 Dye Modules (Models 630 and 630XP) and the Series 700 and 800 KTP/532 or KTP/YAG Surgical Lasers.

The application provides for Photofrin for use in photodynamic therapy for palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, can not be satisfactorily treated with ND-YAG laser therapy.

We also acknowledge receipt of your amendments dated February 3, March 2, April 10, May 12, and June 13, 19 and 20, 1995.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to submit the following information:

CHEMISTRY

The following comments pertain to your amendment dated March 2, 1995.

1. The current HPLC and mass spectroscopic methods measure little more than the total oligomeric content in the mixture. Reference 10 in your amendment showed size exclusion separation of hematoporphyrin diacetate and Photofrin II was achieved on a Fractolgel HW-40 (s) column. In addition, reference 11 cited in the same amendment reported that capillary electrophoresis was able to resolve porphyrin oligomers into distinct peaks. Yet, no attempts to analyze the drug product oligomeric mixture with either method were provided. In summary, the current level of control and characterization of the drug product is not adequate to assure identity, strength, purity and quality, as well as the lot-to-lot uniformity of the drug product. We recommend that an analytical method that, at a minimum, is capable of fingerprinting the oligomeric mixture be developed. This method should be used to establish the release specifications of the drug product and examine its stability as well. (Please refer to Response 7).

2. The batch records (Table 5) showed that the hematoporphyrin dihydrochloride content in the 8 lots range from 78.9% to 88.9%, indicating the need for more stringent process control. A reasonable approach toward establishing a scientifically sound specification for this pivotal intermediate is to determine whether lots with higher hematoporphyrin dihydrochloride contents (such as PC1414, PC1430, E291191, 3V1148BL and 2182-A-1P) produced hematoporphyrin diacetate with more consistent compositions. If batch records prove this to be the case, we recommend that the release specifications of hematoporphyrin dihydrochloride be established on batch records on those lots. (Please refer to Response 10).

3. The responses to Question 13 are not adequate. The justification given for the reaction conditions for the synthesis of the drug substance, i.e., that the reaction product meets release specifications, is not acceptable, because the specifications were established on batch history data produced under the very same conditions. A suitable justification should include data to show that the reaction conditions have been optimized to afford a consistent product. For example, in the synthesis of hematoporphyrin diacetate, data of a controlled study to show that the reaction conditions have been optimized to maximize the

hematoporphyrin diacetate to hematoporphyrin monoacetate ratio should be provided.

4. Please explain why the HPLC protocol specified that the detector be set at nm (see page 177, Vol 8B) while using peak areas measured at 506 nm for calculations. In addition, the porfimer sodium peak area is calculated as the difference of area counts of all detected areas and the sum of peak areas contributed by hematoporphyrin, hydroxyethylvinyldeuteroporphyrins and protoporphyrin. This practice may tend to exaggerate the actual amount of porfimer sodium in the sample. Please explain. (Please refer to response 14).

5. With regards to the diafiltration process of porfimer sodium, justifications to elute the crude material with 120 volume replacements of Water for Injection should be provided; it is noted that there appears to be a substantial amount of monomeric impurities left behind. Furthermore, the flow rate, temperature and other conditions such as protection from bright light exposure as well as any in process controls other than pH monitoring, should be described. (Please refer to Response 15).

6. Specify the proposed additional process controls for the scaled-up drying step in the hematoporphyrin diacetate synthesis. (Please refer to Response 18).

7. The responses to Question 21 are not satisfactory. For the diacetate process, the wide temperature range from 15-30°C should be justified. In addition, no information of reaction completeness tests for both processes were provided.

8. Due to the difficulty in controlling the oligomerization process and characterizing the drug substance mixture, and the absence of a validated purification method for the oligomeric mixture, the proposed specification of hematoporphyrin diacetate should be revised. Batch records of the 12 lots in Table 10 indicated that the hematoporphyrin diacetate content ranged from % to %. Lots PC1012, PC1013, PC1435, PC1436 and PC1437 gave fairly low contents (41.6%, 40.0%, 40.1%, 41.4% and 41.1% respectively); lot PC1112 yielded the most hematoporphyrin diacetate at 51.2%; while the remaining 6 lots

(PC1114, PC1115, PC1189, PC1190, PC1194 and PC1422) gave more uniform results (47.7%, 45.2%, 43.5%, 46.6%, 46.8% and 44.4% respectively). In theory, one would expect that the compositions of porfimer sodium concentrate be directly affected by the composition of this monomeric intermediate. If the batch history records bear out this hypothesis, we recommend that the hematoporphyrin diacetate specifications be established on those lots that afforded the more consistent drug substance. Further analysis of the production history records may help identify parameters in the manufacture of porfimer sodium bulk concentrate that most affect the composition of the product. Finally, batch records should be submitted to justify the proposed 0.8% limit for bromine content. (Please refer to Response 21).

9. Considering the current relatively wide release specifications of the drug substance and the drug product, the practice of designating a production run as the reference standard without any purification and replacing it with a new lot when the first one expires results in the use of a reference material with its purity profile changing periodically for routine comparison of production batches. We recommend that specifications be established for the drug substance reference standard. (Please refer to Response 23).

10. Please identify the peaks eluted at 1.517 min, 5.733 min, 6.917 min, 13.183 min and those eluted between 19.8 min and 20.183 min in the HPLC chromatogram of internal standard S745 (Figure 3, page 50) and explain how to differentiate these peaks from those from Photofrin eluted at the same time. The major component in Photofrin standard S730 (Figure 2, page 49) exhibited a retention time at 19.917 min, whereas the major Photofrin peak in the HPLC trace provided previously (page 114, Vol 1.3) gave a retention time around 15.7 min. Please identify whether this significant shift in retention time is a result of change in column conditions or in mobile phase. (Please refer to Response 27).

11. We have the following comments for Response 28:

    a. The question regarding the possible formation of olefinic degradation products during the manufacturing process and upon storage is not addressed.

b. Please provide data to show that the UV/VIS method (absorption at nm) to assure the photostability of the drug product has been validated.

c. An additional release specification has been proposed for Photofrin to check its relative absorption bands at and nm. Specify the proposed limits of the release specification and test procedures.

d. Data should be submitted to demonstrate that the current HPLC method is capable of detecting degraded products of 3% H_2O_2-stressed Photofrin.

e. The UV/VIS spectroscopic method nm) establishing Photofrin stability towards oxidation, and the limit of detection should be submitted.

12. Because of the method of storage used for the bulk porfimer sodium, freeze-thaw studies should be conducted as soon as possible. Please refer to Deficiencies 1 and 11 cited in this letter for comments on UV/VIS methods, the mass spectroscopic method and HPLC assay.

    The stability of the drug product when stressed with heat, peroxides and bright light should be properly examined after suitable stability-indicating analytical methods have been developed. (Please refer to Response 30).

13. The proposed ranges for the trimer and tetramer ion ratio levels relative to dimers are acceptable. No response has been made to the Agency's request to develop more accurate methods for determining the oligomer size distribution. (Please refer to Response 39h).

14. Sections of the NDA allude to olefinic trimers and tetramers being responsible for some of the more significant adverse events. Response 39i is not acceptable. Analytical methods to properly characterize and assay olefinic oligomers in the drug product mixture should be developed.

15. Please provide data, including monomer impurities, oligomer

content and composition, ester/ether linkage ratios, olefin side chain content and hydroxyethyl side chain content to demonstrate that the preclinical batches, clinical batches and those produced for commercial distribution are equivalent in chemical composition and biological activity. The release specifications and shelf-life specifications, as described in Monographs 18351 and 19857, should be revised after a suitable analytical method, one that can fingerprint the oligomeric mixture, is developed. In addition, because of the adverse events related to olefinic trimers and tetramers, the Photofrin release specification should include an olefin content limit as well. (Please refer to Response 44).

16. We recommend testing intervals of 3, 6, 9, 12, 18, 24 and 36 months for long term stability study and that the assay method employed in the protocol should be validated as stability-indicating (see Comment 1). Cumulative stability data on production batches should be submitted to FDA as part of the annual report required under 21 CFR 314.81(b)(2). (Please refer to Response 46)

The following comments pertain to your amendment of May 12, 1995.

The HPLC assay as described in this submission is not adequate to replace the mouse bioassay currently used to assure the efficacy of PHOTOFRIN batches.

Chemistry comments:

1. Please provide justifications for selecting the 3 types of samples that were used in the development of the bioactivity-indicating HPLC assay (paragraph 2 , page 11).

2. This HPLC assay failed to separate monomeric impurities from the solvent front (Region 1). In addition, it was reported that area increases in Region 3 were observed in HPLC profiles for all stressed Photofrin dry powder samples, indicating that this method is not able to resolve the degraded products from their parent compounds. Justifications should be provided for selecting the described HPLC conditions for release testing.

3. Development of the bioactivity-indicating HPLC assay was only supported by bioassay data and HPLC chromatograms. The bioassay is a pass/fail functional test and HPLC profiles are poorly

resolved. To develop an alternative to the bioassay, other analytical data, including UV/VIS and mass spectroscopic data, should be provided as a measure of the chemical integrity of the oligomeric mixture.

4. Justification should be provided for the proposed acceptable range of area percent values of peaks in Regions 1 and 3 for bioactive Photofrin samples.

5. Table 4 (page 16) gave the bioassay results of reconstituted samples stored frozen at -20°C. It should be noted that the stability of the reconstituted samples under the prescribed conditions has not been fully established. The length of time that the reconstituted samples had been stored should be specified and other data to support the chemical identity of the oligomeric mixture submitted.

6. In one of the stress studies of lyophilized Photofrin, dose response curves indicated a reduction of ED_{50} from mg/kg to mg/kg for the Photofrin vials that had been treated at 80°C in the dark or 40°C under white light (NDA 20-451, Volume 5B, Section 3.2.5.1.2, page 197). However, in a second experiment, when the samples were similarly stressed, no bioactivity enhancement of the treated samples was detected (Study Report AM-93104S, Appendix 2, page 87). Please explain.

Pharmacology comments:

7. Why are two peaks in the PHOTOFRIN chromatogram on page 10 and elsewhere marked Hydroxyethylvinyldeuteroporphyrin (HVD)? Are two similar peaks eluted with this system when HVD standards are chromatographed?

8. The scale of the chromatograms in the submission varies. Was the PHOTOFRIN sample concentration standardized for the HPLC separations?

9. Were the batches used to define and validate the BIHPLC assay manufactured under scheme I, IR or II?

10. You could have prepared the Region 3 reduced sample (appendix

2, page 97) by HPLC purification of PHOTOFRIN similar to the preparation of the Region 3 enriched sample. Hp and HVD together do not appear to account for most of the area in R2. The contribution of the other peaks in PHOTOFRIN chromatographic regions R1 and R2 cannot be determined. The analysis assumes there is no efficacy threshold for some other component of R1 or R2 (non-linear dose response) and that Hp and HVD are completely ineffective. The latter of these two assumptions is not well supported, since this sample had an unexpectedly low ED_{50} , mg/kg). If no PHOTOFRIN activity is associated with Region 2, the intercept of the linear analysis should be statistically equal to 0. Yet, this intercept value is (close to the $1/ED_{50}$ value of the Region 3 reduced sample).

11. The two points from the Region 3 manipulated samples have an inappropriately large influence on your linear analysis. They are far outside the range of the other points and are un-weighted. Also the point at ED_{50} %area = in the photolysis experiment appears an outlier only when the data are analyzed using the reciprocal of ED_{50}. When ED_{50} is plotted directly against %area, this point is an important part of the dose response. Please explain why this point was excluded.

12. If the change in $1/ED_{50}$ from these PHOTOFRIN samples results from the variation of a single linear parameter, the slopes derived from the three experiments should be statistically indistinguishable. The individual slopes are photolysis), (pyrolysis) and (R3-manipulated). The Student's-t statistic for the slopes from the photolysis and pyrolysis data is significantly larger than the tabular t value indicating that the slopes are significantly different. These lines are not parallel. The slopes and intercepts for all three lines appear from the graph to be different. Please explain why these experiments were combined for this analysis? A linear analysis can sometimes be used to describe a dose response within the pseudo-linear region of the curve when the curve is well defined. Nevertheless, the photolysis experiments do not vary %area R3 across a sufficiently wide range to adequately define the upper and lower limits of a dose response curve. The pyrolysis experiments demonstrate no dose response and the manipulated R3 samples are probably not measuring the same pseudo-linear phenomenon. The relationship between ED_{50} and

%area R3 will probably be better analyzed as a reverse-sigmoidal dose response where integrated %area is the dose and ED_{50} is the response. A replot of the raw data from the pyrolysis experiment suggests such a relationship. You should use such a dose response analysis to specify acceptable limits for the %area from lower (ED_{50} = x mg/kg) and upper (ED_{50} = y mg/kg) dose response values.

13. Since a dose response relationship probably exists between some component of Region 3, what is the rationale for using three standard deviations from the batch-to-batch mean %area Region 3 to define the limits for batch acceptability? How do these limits relate to the dose response? Batches P91-164 and P91-163 had %area Region 3 values of 32.3 and 31.1 respectively in the experiments used to calculate this batch-to-batch mean (Appendix 1, page 81). These batches had %area Region 3 values of 35 and 36 respectively in subsequent experiments to determine the dose response (Appendix 2, page 102). What caused this difference? Using the limits defined from the batch-to-batch mean and standard deviation of Appendix 1, samples with only 2% higher %area Region 3 values than these obtained for P91-164 and P91-163 in Appendix 2 would be rejected.

14. In future submissions please include the raw data from the ED_{50} experiments. How many points did you use to determine ED_{50}? How many animals were in each dose group?

15. The results of these PHOTOFRIN degradation studies (photolysis and pyrolysis) imply that Region 3 of the chromatogram contains at least two components that significantly affect the integrated %area. The concentration of one component increases with pyrolysis of the lyophilized powder yet does not influence PDT efficacy. That of another decreases with photolysis of reconstituted PHOTOFRIN and is central to the mechanism of PDT. The current HPLC assay cannot distinguish between these two components and thus cannot predict batch-to-batch efficacy or uniformity. For example, a batch exposed to excess heat might be rejected because the %area of Region 3 was to great, yet the batch would pass the bioassay This finding is not discouraging. It suggests that better chromatographic separation or defining smaller chromatographic regions may distinguish the component

within R3 that correlates with activity. This method cannot as yet replace the bioassay used to assure the efficacy of each batch of PHOTOFRIN, but such a replacement is probably attainable.

MICROBIOLOGY

Please provide the additional or clarifying information, described below, to support the sterilization process validation information portion of your NDA and fulfill the post-approval commitments. Although you have cited the FDA's "GUIDELINE FOR SUBMITTING DOCUMENTATION FOR STERILIZATION PROCESS VALIDATION IN APPLICATIONS FOR HUMAN AND VETERINARY DRUG PRODUCTS (DECEMBER 3, 1993)" (p 4, 05-1 3-94 amendment to the NDA) we request that you use this cited format to prepare your response to these requests for further information. Manufacturing operations, filling process, monitoring activities, batch records, physical lay-out (and other items below) need to be more completely described in order to complete the review and evaluation of the microbiological quality and sterility assurance of the subject drug product.

If these types of information have been provided to more recently prepared NDAs, the information may be referenced. Please provide for a 'desk copy' for microbiology review purposes.

The following concern your descriptions for Product Manufacturing Process:

a. What is the pH of the diluted sample in NaOH, and

b. is the pH of the resulting sample solution adjusted to neutrality prior to filtration for the microbial limits test?

2. Part of the manufacturing procedure for profimer sodium bulk concentrate (Vol 3, p 195-196) includes filtering through a μ

filter into a polycarbonate bottle. The resulting product solution is then tested by (Vol 4, p 1-1 5) whose specification for 'Microbial Limit' is not more than CFU/ mL of concentrate. Please define exactly what the 'sample" is that is being tested for the microbial limit by both Methods of

3. The reference cited for Vol 4, p 1-15) namely, a 'Special Microbiological Study Report: PHOTOFRIN 11 Bulk Liquid, Qualification of Total Aerobic Count: dated 1.4.94 [issued to qualify the cited method identified as "Microbial Limits" (Vol 4, p 4)] should be provided to clarify the microbiological methods used for Photofrin (porfimer sodium).

The following concern your Documentation for Sterilization Process Validation.

Some additional information is necessary. Also, the information provided in General Facilities Description (Attachment 3, Section 3.2.3.5) does not clearly describe the manufacturing and filling process or monitoring activities sufficiently to completely evaluate the microbiological quality and sterility assurance of the subject drug product.

1. The specific acceptance criteria for the validation studies conducted for the should be provided. Summaries of the sterilization process validation protocols, studies, and data that specify the acceptance criteria, and demonstrate that the acceptance criteria were met, should be provided to the application.

2. All product-contact equipment needs to be clearly identified by name and room location. The product, personnel, and component flow sequence from bulk formulation to filling to packaging needs to be provided.

The following concern the Aseptic Fill Manufacturing Process and Environmental monitoring program.

1. Please provide information regarding the specific room and locations within the room where samples are obtained. A sketch or diagram (blueprints are not necessary) with the sampling

location indicated would be helpful.

2. The equipment used in the aseptic fill manufacturing process needs to be adequately identified and described in the application so that samples obtained from (or near?) product-contact equipment" are clearly understood.

3. Microbiological protocols, methods, and data generated by this type of environmental monitoring should be provided. For example, quantitative limits are given for swab samples obtained from surfaces, but there is no information to indicate that the 'swab sample' is either obtained or cultured in a quantitative fashion.

4. There appear to be occasional surveys for 'mold' and 'anaerobes' (p 14, 15) but no protocols, methods, or data generated by this type of monitoring are provided. Since routine yeast and mold monitoring should be part of the environmental monitoring program, please supply or reference this information to the application. Representative results from past surveys for 'mold' and 'anaerobes' should be provided.

5. Alert limits are not provided. The cited "appendix from SOP no. 139..... action limits for each room" (p 14) was not located.

The following concern the Sterilization of Drug Product by Filtration.

Additional information is needed to support the application. You state that the drug product Photofrin (porfimer sodium) is filtered prior to filling and that the filtration apparatus is pre- and post-tested at psig (bubble point; p 104-105, Volume 5A, for example), but you have provided no further information concerning the validation of the sterilization process by filtration, nor have you referenced its location elsewhere.

1. We request that you provide the following information to the application as part of the recommended information discussed in 'GUIDELINE FOR SUBMITTING DOCUMENTATION FOR STERILIZATION PROCESS VALIDATION IN APPLICATIONS FOR HUMAN AND VETERINARY DRUG PRODUCTS (DECEMBER 3, 1993) to demonstrate and document validation of the sterilizing filtration process.

a. Complete protocol for testing the sterilizing efficacy of the filtration system used in the manufacture of the subject drug product should be submitted. This should include demonstration of its efficacy relative to the subject drug product.

b. Identification of manufacturer and model number of the complete filtration apparatus, i. e., housing, cartridge or disk should be submitted. Validation of the sterilizing efficacy of "alternate or other suitable equipment' is highly recommended. Applicants intending to 'mix' components, i. e., one vendor's housing used with another vendor's cartridge, disk, or other configuration, should provide information demonstrating the sterilizing efficacy of these combinations.

c. Identification of the parameters used in the validation testing protocols should be provided. For example, fluid used, flow rate, pressure, or other physical parameters; identification of microbial species used for challenge, its culture and challenge preparation methods.

d. Similar identification and methods information for the test controls should be provided.

Before the application may be approved, it will also be necessary for you to submit revised draft labeling. The labeling should include the revisions enclosed with this letter.

We note that your June 13 and 19, 1995 letters included the following commitments:

1. The limitation of recommended use of PHOTOFRIN to patients with complete obstructions and partial obstructions only where ND-YAG laser cannot be used is based on safety concerns. There has not, however, been a trial carried out prospectively in the latter population to define effectiveness rates. You have agreed to design and perform a phase 4 single-arm study to assess the efficacy (dysphagia response) and safety of PHOTOFRIN-PDT in patients with partially obstructing esophageal cancer who, in the opinion of their physician, can not be satisfactorily treated with

ND-YAG laser therapy. The specifics of the study design and patient population will be agreed upon with the Agency prior to finalization of the protocol;

2. to conduct a phase 4 acute toxicity study of the current formulation of Photofrin in rats which will include doses that are clearly toxic and include one dose that causes some mortality. The study will include assessment of gross pathology and histopathology; and

3. to conduct phase 4 studies to gather further pharmacokinetic data in patients with hepatic impairment and in patients who have received more than one course of therapy. Pharmacokinetics will also be characterized in male and female patients.

We suggest that you may wish to re-test the genotoxicity of Photofrin. Our concern is not based on the labeled use for patients with advanced esophageal cancer, but on the clear potential for use of PHOTOFRIN PDT in non-malignant diseases. Data suggests that Photofrin with and without light may cause significant sister chromatid exchange or HGPRT mutations in Chinese Hamster Ovary cells. If conducted, GLP genotoxicity studies should be performed at Photofrin concentrations that cause significant cytotoxicity (70 to 90% cell death for the maximum dose). Such studies should be done with at least three and preferably five concentrations. The cells should be exposed to Photofrin for five to eight hours in the dark. The Photofrin solution then should be washed from the cells before irradiation so that the cells are not shielded by the Photofrin absorbance. Sister chromatid exchange or HGPRT mutation should also be determined in non-irradiated cells at cytotoxic concentrations.

We also recommend that you characterize the mass balance of Photofrin using maximum allowable radioactive dose of the drug and monitoring for as long as the radioactivity counts remain above background.

Please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Oncology Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and
Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any deficiencies that may occur.

We remind you that a satisfactory inspection of your manufacturing facilities for conformance with current good manufacturing practices (CGMP) is required before this application may be approved.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of the invoice.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Paul Zimmerman
Consumer Safety Officer
Telephone: (301) 594-5775

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Labeling Revisions

cc:
Original NDA 20-451
HFD-150/Div. Files
HFD-2/M.Lumpkin
HFD-80
HFD-100
HFD-150/P.Zimmerman
HFD-150/GWilliams
HFD-150/AMurgo
HFD-150/YHsieh
HFD-150/CHoiberg
HFD-150/RJustice
HFD-150/JDeGeorge
HFD-150/DMcGuinn
HFD-150/RWood
HFD-426/MMehta
HFD-426/ARahman
HFD-713/SWilson
HFD-713/AKoutsoukos
HFZ-410/RFelter
HFD-150/DPease
HFD-160/PCooney
HFD-160/CVincent
HFD-643/NSager
DISTRICT OFFICE
HFD-240/S.Sherman (with draft labeling)
HFD-638 (with draft labeling)
drafted: PFZ/June 7, 1995/c:\wpfiles\20451.nda\letters\aeletter
r/d Intials: YHsieh/7-6-95
RWood/7-6-95
DMcGuinn/7-6-95
JDeGeorge/7-6-95
AKoutsoukos/7-6-95
SWilson/7-5-95
ARahman/7-5-95
MMehta/7-5-95
RJustice for GWilliams/7-6-95
RJustice/7-6-95
LVaccari for DPease/7-6-95
RJustice for CHoiberg/7-6-95
Final Type: PZimmerman/7-7-95/7-13-95

APPROVABLE (AE)

Labeling Revisions for the April 12, 1994 draft labeling

1. In the Pharmacology subsection of the CLINICAL PHARMACOLOGY section, the seventh sentence should be modified as follows:

   Intracellular PHOTOFRIN-PDT damage results from radical reactions. Radical initiation may occur after PHOTOFRIN absorbs light to form a porphyrin excited state. Spin transfer from PHOTOFRIN to molecular oxygen may then generate singlet oxygen. Subsequent radical reactions can form superoxide and hydroxyl radicals.

2. The pharmacokinetic parameters and information obtained from study D73 P503 can not be properly validated due to lack of assay specificity. The data from PK Report No. 2 (Vol.32, p. 200) is also inconclusive due to lack of assay specificity and due to inadequate duration of sampling. The estimated pharmacokinetic parameters from PK Report No. 4 appear to be more reliable as the HPLC assay methodology used in that study separated porfimer sodium from the other porphyrin related compounds in plasma. The study represented the pharmacokinetics of oligomers present in the drug product. Therefore, the data generated in that study should be used in the package insert until better data become available.

   The following should be substituted for the Pharmacokinetics subsection of the CLINICAL PHARMACOLOGY section:

   " Following a 2 mg/kg dose of porfimer sodium to 4 male cancer patients, the average peak plasma concentration was 15 ± 3 μ/mL, the elimination half-life was 250 ± 285 hour, the steady-state volume of distribution was 0.49 ± 0.28 L/kg, and the total plasma clearance was 0.051 ± 0.035 mL/min/kg. The mean plasma concentration at 48 hours was 2.6 ± 0.4 μg/mL. The influence of impaired hepatic function on PHOTOFRIN disposition has not been evaluated.

   PHOTOFRIN was approximately 90% protein bound in human serum, studied *in vitro*. The binding was independent of concentration over the concentration range of 20-100 μg/mL."

3. No mass-balance study was provided to substantiate the following statement in the Pharmacokinetics subsection of the CLINICAL PHARMACOLOGY section of the package insert:

"Excretion of porfimer sodium components occurs primarily via the fecal route."

The statement is based on studies conducted in mouse, rat, and dog using doses different from the dose suggested for human use. The statement should be deleted.

4. In the Clinical Studies section, the phrase "Phase III" should be removed from both places it appears, and the text of the first paragraph should be modified slightly, as follows:

"A multicenter, randomized, open-label clinical trial was conducted comparing the effects of PDT with PHOTOFRIN and controlled uniform laser light to thermal ablation therapy using Nd:YAG laser on tumor mass for local palliation of dysphagia in 236 patients with partially obstructing esophageal carcinoma. Each course of PDT with PHOTOFRIN consisted of one injection of the drug (2 mg/kg administered as a slow intravenous injection over 3-5 minutes) followed by up to two nonthermal laser light applications (630 nm administered at a dose of 300 J/cm of tumor), the first application of light occurring 40-50 hours after injection, and the second at 96-120 hours. Additional courses of PDT with PHOTOFRIN were allowed after one month, up to a total of 3. Nd:YAG laser therapy was administered with a laser power setting of 15-90 W with a pulse duration of 0.5-4.0 seconds per pulse. The total energy dose ranged from 500-30,000 J/session, depending on the tumor volume. Repeat Nd:YAG laser sessions, with no limit on the number of applications, were given until maximal anticipated tumor debulking and palliation of dysphagia were achieved. Course 1 efficacy results, based on all 236 randomized patients, are provided in Table 1. Based on all courses, nine PDT-treated patients and two Nd:YAG-treated patients had no visible evidence of tumor and were considered to be in complete response (CR). In six PDT-treated patients and two Nd:YAG-treated patients, CR was verified by pathology."

Concerning Table 1 (Course 1 Efficacy Results in the Randomized Trial) in the Clinical Studies subsection of the CLINICAL PHARMACOLOGY section, definitions of the column headings of the table should be added as footnotes. The asterisk for statistical significance should be removed. A footnote for the column with

Time to palliation failure should mention that the amount of missing data prohibited a statistical comparison of efficacy on the 2 arms and the results should be interpreted with caution.

Data on one-month dysphagia grade changes should be included as part of the efficacy presentation (e.g., in Table 1).

5. In the INDICATIONS AND USAGE section, the indication should be "Photodynamic therapy with PHOTOFRIN is indicated for palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, can not be satisfactorily treated with ND-YAG laser therapy."

6. In the WARNINGS section, the sentence, "After 30 days, patients may expose a small area of skin (finger, dorsum of hand) to the sun for 5 minutes to test for residual photosensitivity. If significant erythema or blistering results,...." suggests testing skin for photosensitivity but gives no guidelines regarding when the test can be considered complete; such guidelines should be included in the labeling (and supported in an amendment).

7. There was no formal pharmacokinetic based drug interaction study performed. Therefore, the Drug Interactions subsection of the PRECAUTIONS section should begin with the following sentence.

"There have been no formal interaction studies of PHOTOFRIN and any other drugs."

8. In the Drug Interactions subsection of the PRECAUTIONS section, the following text on combination studies in animals should be removed.

Animal or *in vitro* studies involving combination therapy with PDT and standard antineoplastic agents (including doxorubicin, mitomycin C, and BCG for bladder cancer, and mitomycin C in a colon cancer cell line) resulted in an increase in effectiveness compared with single therapies. Similarly, combinations of PDT with PHOTOFRIN and different photosensitizers with different biodistribution properties (including tetraphenylporphine sulfonate) resulted in enhanced tumor eradication in a murine mammary

tumor model.

9. In the Drug Interactions subsection of the PRECAUTIONS section, the second paragraph should be modified as follows:

PHOTOFRIN-PDT causes direct intracellular damage by initiating radical chain reactions that damage intracellular membranes and mitochondria. Tissue damage also results from ischemia secondary to vasoconstriction, platelet activation and aggregation and clotting. Research in animals and in cell culture has suggested that many drugs could influence the effects of PDT. There are no human data that support or rebut these possibilities.

Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulfoxide, b-carotene, ethanol, formate and mannitol would be expected to decrease PDT activity. Preclinical data also suggest that tissue ischemia, allopurinol, calcium channel blockers and some prostaglandin synthesis inhibitors could interfere with PHOTOFRIN PDT. Drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A_2 inhibitors, could decrease the efficacy of PDT. Glucocorticoid hormones given before or concomitant with PDT may decreased the efficacy of the treatment.

10. The Carcinogenesis, Mutagenesis, Impairment of Fertility subsection of the PRECAUTIONS section should be modified as follows:

No long term studies have been conducted to evaluate the carcinogenic potential of PHOTOFRIN. *In vitro*, PHOTOFRIN-PDT, with or without S9 activation, did not cause mutations in the Ames test, nor did it cause chromosome aberrations or mutations (HGPRT locus) in Chinese hamster ovary (CHO) cells. PHOTOFRIN caused <2 fold, but significant, increases in sister chromatid exchange in CHO cells irradiated with visible light and a 3 fold increase in Chinese hamster lung fibroblasts irradiated with near UV light. PHOTOFRIN-PDT caused an increase in thymidine kinase mutants and DNA-protein cross-links in mouse L5178Y cells, but not mouse LYR83 cells. PHOTOFRIN-PDT caused a light-dose dependant increase in DNA-strand breaks in malignant human cervical carcinoma cells, but not in normal cells. The mutagenicity of PHOTOFRIN without light has not been adequately determined.

In vivo, PHOTOFRIN did not cause chromosomal aberrations in the mouse micronucleus test.

PHOTOFRIN given to male and female rats intravenously, at 4 mg/kg/d (0.32 times the clinical dose on a mg/m^2 basis) before conception and through day 7 of pregnancy caused no impairment of fertility, but did cause hypertrophy of the ovaries and testes and decreased body weight in the parent rats.

11. The Pregnancy subsection of the PRECAUTIONS section should be modified in accord with the following:

PHOTOFRIN given to rat dams during fetal organogenesis intravenously at 8 mg/kg/d (0.64 times the clinical dose on a mg/m^2 basis) caused no major malformations or developmental changes. This dose caused maternal and fetal toxicity resulting in increased resorptions, delayed ossification, decreased litter size, and reduced fetal weight. PHOTOFRIN caused no major malformations when given to rabbits intravenously during organogenesis at 8 mg/kg/d (1.5 times the clinical dose on a mg/m^2 basis).

PHOTOFRIN given to rats during late pregnancy through lactation intravenously at 4 mg/kg/d (0.32 times the clinical dose on a mg/m^2 basis), caused a reversible decrease in growth of offspring.

12. In the Use in Elderly Patients subsection of the PRECAUTIONS section, the statement, "PDT with PHOTOFRIN is as safe and effective in elderly patients as in younger patients." is somewhat overstated and should be modified to say:

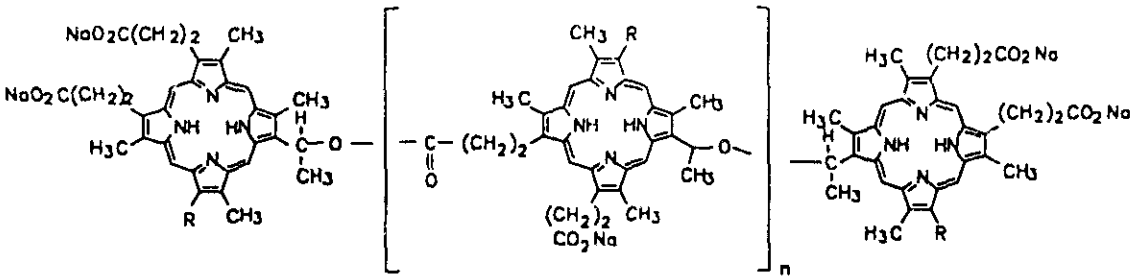
"Almost 80% of the patients treated with PDT using PHOTOFRIN in clinical trials were over 60 years of age. There was no apparent difference in effectiveness or safety in these patients compared to younger people. Dose modification based on age is not required."

13. The Endobronchial Carcinoma subsection of the ADVERSE REACTIONS section should be removed.

PHOTOFRIN® (sterile porfimer sodium) for Injection

DESCRIPTION

PHOTOFRIN® (porfimer sodium) for Injection is a photosensitizing agent used in the photodynamic therapy (PDT) of tumors. Following reconstitution of the freeze-dried product with 5% Dextrose Injection (USP) or 0.9% Sodium Chloride Injection (USP), it is injected intravenously. This is followed 40–50 hours later by illumination of the tumor with laser light (630 nm wavelength). PHOTOFRIN® is not a single chemical entity; it is a mixture of oligomers formed by ether and ester linkages of up to eight porphyrin units. It is a dark red to reddish brown cake or powder. Each vial of PHOTOFRIN® contains 75 mg of porfimer sodium as a sterile freeze-dried cake or powder. Hydrochloric Acid and/or Sodium Hydroxide may be added during manufacture to adjust pH. There are no preservatives or other additives. The structural formula below is representative of the components present in PHOTOFRIN®.



n = 0–6

R = $-CH(OH)CH_3$ or $-CH=CH_2$

CLINICAL PHARMACOLOGY

Pharmacology

The cytotoxic and antitumor actions of PHOTOFRIN® are light and oxygen dependent. Photodynamic therapy (PDT) with PHOTOFRIN® is a two-stage process. The first stage is the intravenous injection of PHOTOFRIN®. Clearance from a variety of tissues occurs over 40–72 hours, but tumors, skin, and organs of the reticuloendothelial system (including liver and spleen) retain PHOTOFRIN® for a longer period. Illumination with 630 nm wavelength laser light constitutes the second stage of therapy. Tumor selectivity in treatment occurs through a combination of selective retention of PHOTOFRIN® and selective delivery of light. Cellular damage caused by PHOTOFRIN® PDT is a consequence of the propagation of radical reactions. Radical initiation may occur after PHOTOFRIN® absorbs light to form a porphyrin excited state. Spin transfer from PHOTOFRIN® to molecular oxygen may then generate singlet oxygen. Subsequent radical reactions can form superoxide and hydroxyl radicals. Tumor death also occurs through ischemic necrosis secondary to vascular occlusion that appears to be partly mediated by thromboxane A_2 release. The laser treatment induces a photochemical, not a thermal, effect.

Pharmacokinetics

Following a 2 mg/kg dose of porfimer sodium to 4 male cancer patients, the average peak plasma concentration was 15 ± 3 μg/mL, the elimination half-life was 250 ± 285 hours, the steady-state volume of distribution was 0.49 ± 0.28 L/kg, and the total plasma clearance was 0.051 ± 0.035 mL/min/kg. The mean plasma concentration at 48 hours was 2.6 ± 0.4 μg/mL. The influence of impaired hepatic function on PHOTOFRIN® disposition has not been evaluated.

PHOTOFRIN® was approximately 90% protein bound in human serum, studied in vitro. The binding was independent of concentration over the concentration range of 20–100 μg/mL.

Clinical Studies

PDT with PHOTOFRIN® was utilized in a multicenter, single-arm study in 17 patients with completely obstructing esophageal carcinoma. Each course of PDT with PHOTOFRIN® consisted of one injection of the drug (2 mg/kg administered as a slow intravenous injection over 3–5 minutes) followed by up to two nonthermal laser light applications (630 nm administered at a dose of 300 J/cm of tumor), the first application of light occurring 40–50 hours after injection. Debridement of residua was performed via endoscopy 96–120 hours after injection, after which any residual tumor could be retreated with a second laser light application at the same dose used for the initial treatment. Additional courses of PDT with PHOTOFRIN® were allowed after 1 month, up to a total of 3. Assessments were made at 1 week and 1 month after the last treatment procedure. As shown in Table 1, after a single course of therapy, 94% of patients obtained an objective tumor response and 76% of patients experienced some palliation of their dysphagia. On average, before treatment these patients had difficulty swallowing liquids, even saliva. After one course of therapy, there was a statistically significant improvement in mean dysphagia grade (1.5 units, $p < 0.05$) and 13 of 17 patients could swallow liquids without difficulty 1 week and/or 1 month after treatment. Based on all courses, three patients achieved a complete tumor response (CR). In two of these patients, the CR was documented only at Week 1 as they had no further assessments. The third patient achieved a CR after a second course of therapy, which was supported by negative histopathology and maintained for the entire follow-up of 6 months.

Of the 17 treated patients, 11 (65%) received clinically important benefit from PDT. Clinically important benefit was defined hierarchically ~~by obtaining~~ as a complete tumor response (3 patients), ~~achieving~~ achievement of normal swallowing (2 patients went from Grade 5 dysphagia to Grade 1), or ~~achieving a dramatic~~ achievement of a marked improvement of two or more grades of dysphagia with minimal adverse reactions (6 patients). The median duration of benefit in these patients was 69+ days. Duration of benefit was calculated only for the period with documented evidence of improvement. All of these patients were still in response at their last assessment and, therefore, the estimate of 69 days is conservative. The median survival for these 11 patients was 115 days.

TABLE 1. Course 1 Efficacy Results in Patients with Completely Obstructing Esophageal Cancer

	PDT n=17
IMPROVEMENT[a] IN DYSPHAGIA (% of Patients)	
Week 1	71%
Month 1	47%
Any assessment[b]	76%
MEAN DYSPHAGIA GRADE[c] AT BASELINE	4.6
MEAN IMPROVEMENT[c] IN DYSPHAGIA GRADE (units)	
Week 1	1.4
Month 1	1.5
OBJECTIVE TUMOR RESPONSE[d] (% of Patients)	
Week 1	82%
Month 1	35%[e]
Any assessment[b]	94%
MEAN NUMBER OF LASER APPLICATIONS PER PATIENT	1.4

a Patients with at least a one-grade improvement in dysphagia grade
b Week 1 or Month 1
c Dysphagia Scale: Grade 1 = normal swallowing, Grade 2 = difficulty swallowing some hard solids; can swallow semisolids, Grade 3 = unable to swallow any solids; can swallow liquids, Grade 4 = difficulty swallowing liquids, Grade 5 = unable to swallow saliva.
d CR+PR, CR = complete response (absence of endoscopically visible tumor), PR = partial response (appearance of a visible lumen)
e Eight of the 17 treated patients did not have assessments at Month 1.

INDICATIONS AND USAGE

Photodynamic therapy with PHOTOFRIN® is indicated for palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with Nd:YAG laser therapy.

CONTRAINDICATIONS

PHOTOFRIN® is contraindicated in patients with porphyria or in patients with known allergies to porphyrins.

PDT is contraindicated in patients with an existing tracheoesophageal or bronchoesophageal fistula.

PDT is contraindicated in patients with tumors eroding into a major blood vessel.

WARNINGS

If the esophageal tumor is eroding into the trachea or bronchial tree, the likelihood of tracheoesophageal or bronchoesophageal fistula resulting from treatment is sufficiently high that PDT is not recommended.

Following injection with PHOTOFRIN® precautions must be taken to avoid exposure of skin and eyes to direct sunlight or bright indoor light (see PRECAUTIONS, Information for Patients).

(Special Precautions and

PRECAUTIONS

General Precautions and

Information for Patients

Photosensitivity

All patients who receive PHOTOFRIN® will be photosensitive and must observe precautions to avoid exposure of skin and eyes to direct sunlight or bright indoor light (from examination lamps, including dental lamps, operating room lamps, unshaded light bulbs at close proximity, etc.) for 30 days. The photosensitivity is due to residual drug which will be present in all parts of the skin. Exposure of the skin to ambient indoor light, however, is beneficial because the remaining drug will be inactivated gradually and safely through a photobleaching reaction. Therefore, patients should not ~~be kept~~ stay in a darkened room during this period and should be encouraged to expose their skin to ambient indoor light. The level of photosensitivity will vary for different areas of the body, depending on the extent of previous exposure to light. Before exposing any area of skin to direct sunlight or bright indoor light, the patient should test it for residual photosensitivity. A small area of skin should be exposed to sunlight for 10 minutes. If no photosensitivity reaction (erythema, edema, blistering) occurs within 24 hours, the patient can gradually resume normal outdoor activities, initially continuing to exercise caution and gradually allowing increased exposure. If some photosensitivity reaction occurs with the limited skin test, the patient should continue precautions for another 2 weeks before retesting. The tissue around the eyes may be more sensitive, and therefore, it is not recommended that the face be used for testing. If patients travel to a different geographical area with greater sunshine, they should retest their level of photosensitivity. UV (ultraviolet) sunscreens are of no value in protecting against photosensitivity reactions because photoactivation is caused by visible light.

Ocular Sensitivity

Ocular discomfort, commonly described as sensitivity to sun, bright lights, or car headlights, has been reported in patients who received PHOTOFRIN®. For 30 days, when outdoors, patients should wear dark sunglasses which have an average white light transmittance of $< 4\%$.

dark print

Chest pain

As a result of PDT treatment, patients may complain of substernal chest pain because of inflammatory responses within the area of treatment. Such pain may

be of sufficient intensity to warrant the short-term prescription of opiate analgesics.

Avoidance of Pregnancy
Women of childbearing potential should practice an effective method of contraception during therapy (see Pregnancy).

Drug Interactions

There have been no formal interaction studies of PHOTOFRIN® and any other drugs. However, it is possible that concomitant use of other photosensitizing agents (e.g., tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide diuretics, and griseofulvin) could increase the photosensitivity reaction.

PHOTOFRIN® PDT causes direct intracellular damage by initiating radical chain reactions that damage intracellular membranes and mitochondria. Tissue damage also results from ischemia secondary to vasoconstriction, platelet activation and aggregation and clotting. Research in animals and in cell culture has suggested that many drugs could influence the effects of PDT, possible examples of which are described below. There are no human data that support or rebut these possibilities.

Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulfoxide, b-carotene, ethanol, formate and mannitol would be expected to decrease PDT activity. Preclinical data also suggest that tissue ischemia, allopurinol, calcium channel blockers and some prostaglandin synthesis inhibitors could interfere with PHOTOFRIN® PDT. Drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g., thromboxane A_2 inhibitors, could decrease the efficacy of PDT. Glucocorticoid hormones given before or concomitant with PDT may decrease the efficacy of the treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies have been conducted to evaluate the carcinogenic potential of PHOTOFRIN®. In vitro, PHOTOFRIN® PDT did not cause mutations in the Ames test, nor did it cause chromosome aberrations or

mutations (HGPRT locus) in Chinese hamster ovary (CHO) cells. PHOTOFRIN® caused < 2-fold, but significant, increases in sister chromatid exchange in CHO cells irradiated with visible light and a 3-fold increase in Chinese hamster lung fibroblasts irradiated with near UV light. PHOTOFRIN® PDT caused an increase in thymidine kinase mutants and DNA-protein cross-links in mouse L5178Y cells, but not mouse LYR83 cells. PHOTOFRIN® PDT caused a light-dose dependant increase in DNA-strand breaks in malignant human cervical carcinoma cells, but not in normal cells. The mutagenicity of PHOTOFRIN® without light has not been adequately determined. In vivo, PHOTOFRIN® did not cause chromosomal aberrations in the mouse micronucleus test.

PHOTOFRIN® given to male and female rats intravenously, at 4 mg/kg/d (0.32 times the clinical dose on a mg/m^2 basis) before conception and through Day 7 of pregnancy caused no impairment of fertility. In this study, long-term dosing with PHOTOFRIN® caused discoloration of testes and ovaries and hypertrophy of the testes. PHOTOFRIN® also caused decreased body weight in the parent rats.

Pregnancy: Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. PHOTOFRIN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PHOTOFRIN® given to rat dams during fetal organogenesis intravenously at 8 mg/kg/d (0.64 times the clinical dose on a mg/m^2 basis) for 10 days caused no major malformations or developmental changes. This dose caused maternal and fetal toxicity resulting in increased resorptions, decreased litter size, delayed ossification, and reduced fetal weight. PHOTOFRIN® caused no major malformations when given to rabbits intravenously during organogenesis at 4 mg/kg/d (0.65 times the clinical dose on a mg/m^2 basis) for 13 days. This dose caused maternal toxicity resulting in increased resorptions, decreased litter size, and reduced fetal body weight.

PHOTOFRIN® given to rats during late pregnancy through lactation intravenously at 4 mg/kg/d (0.32 times the clinical dose on a mg/m^2 basis) for at least 42 days caused a reversible decrease in growth of offspring. Parturition was unaffected.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from PHOTOFRIN®, women receiving PHOTOFRIN® must not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Use in Elderly Patients

Almost 80% of the patients treated with PDT using PHOTOFRIN® in clinical trials were over 60 years of age. There was no apparent difference in effectiveness or safety in these patients compared to younger people. Dose modification based upon age is not required.

ADVERSE REACTIONS

Systemically induced effects associated with PDT with PHOTOFRIN® consist of photosensitivity and mild constipation. All patients who receive PHOTOFRIN® will be photosensitive and must observe precautions to avoid sunlight and bright indoor light (see PRECAUTIONS). Photosensitivity reactions (mostly mild erythema on the face and hands) occurred in approximately 20% of patients treated with PHOTOFRIN®.

Most toxicities associated with this therapy are local effects seen in the region of illumination and occasionally in surrounding tissues. The local adverse reactions are characteristic of an inflammatory response induced by the photodynamic effect.

Esophageal Carcinoma

The following adverse events were reported in at least 5% of patients treated with PHOTOFRIN® PDT, who had completely or partially obstructing esophageal cancer. Table 2 presents data from 88 patients who received the currently marketed formulation. The relationship of many of these adverse events to PDT with PHOTOFRIN® is uncertain.

TABLE 2. Adverse Events Reported in 5% or More of Patients with Obstructing Esophageal Cancer
(Page 1 of 3)

BODY SYSTEM/ Adverse Event	Number (%) of Patients PDT with PHOTOFRIN® n=88	
Patients with at Least One Adverse Event	84	(95)
AUTONOMIC NERVOUS SYSTEM		
Hypertension	5	(6)
Hypotension	6	(7)
BODY AS A WHOLE		
Asthenia	5	(6)
Back pain	10	(11)
Chest pain	19	(22)
Chest pain (substernal)	4	(5)
Edema generalized	4	(5)
Edema peripheral	6	(7)
Fever	27	(31)
Pain	19	(22)
Surgical complication	4	(5)
CARDIOVASCULAR		
Cardiac failure	6	(7)
GASTROINTESTINAL		
Abdominal pain	18	(20)
Constipation	21	(24)
Diarrhea	4	(5)
Dyspepsia	5	(6)
Dysphagia	9	(10)
Eructation	4	(5)
Esophageal edema	7	(8)

TABLE 2. Adverse Events Reported in 5% or More of Patients with Obstructing Esophageal Cancer
(Page 2 of 3)

BODY SYSTEM/ Adverse Event	Number (%) of Patients PDT with PHOTOFRIN® n=88	
GASTROINTESTINAL (continued)		
Esophageal tumor bleeding	7	(8)
Esophageal stricture	5	(6)
Esophagitis	4	(5)
Hematemesis	7	(8)
Melena	4	(5)
Nausea	21	(24)
Vomiting	15	(17)
HEART RATE/RHYTHM		
Atrial fibrillation	9	(10)
Tachycardia	5	(6)
METABOLIC & NUTRITIONAL		
Dehydration	6	(7)
Weight decrease	8	(9)
PSYCHIATRIC		
Anorexia	7	(8)
Anxiety	6	(7)
Confusion	7	(8)
Insomnia	12	(14)
RED BLOOD CELL		
Anemia	28	(32)
RESISTANCE MECHANISM		
Moniliasis	8	(9)

TABLE 2. Adverse Events Reported in 5% or More of Patients with Obstructing Esophageal Cancer
(Page 3 of 3)

BODY SYSTEM/ Adverse Event	PDT with PHOTOFRIN® n=88 Number (%) of Patients	
RESPIRATORY		
Coughing	6	(7)
Dyspnea	18	(20)
Pharyngitis	10	(11)
Pleural effusion	28	(32)
Pneumonia	16	(18)
Respiratory insufficiency	9	(10)
Tracheoesophageal fistula	5	(6)
SKIN & APPENDAGES		
Photosensitivity reaction	17	(19)
URINARY		
Urinary tract infection	6	(7)

Location of the tumor was a prognostic factor for three adverse events: upper-third of the esophagus (esophageal edema), middle-third (atrial fibrillation), and lower-third, the most vascular region (anemia). Also, patients with large tumors (>10 cm) were more likely to experience anemia. Two of 17 patients with complete esophageal obstruction from tumor experienced esophageal perforations which were considered to be possibly treatment associated; these perforations occurred during subsequent endoscopies.

Serious and other notable adverse events observed in less than 5% of PDT-treated patients in the clinical studies include the following; their relationship to therapy is uncertain. In the gastrointestinal system, esophageal perforation, gastric ulcer, , ileus, jaundice, and peritonitis have occurred. Sepsis has been reported occasionally. Cardiovascular events have included angina

delete these;
use no meaning
cardiac failure is in table

pectoris, bradycardia, , myocardial infarction, sick sinus syndrome, and supraventricular tachycardia. Respiratory events of bronchitis, bronchospasm, laryngotracheal edema, pneumonitis, pulmonary hemorrhage, pulmonary edema, respiratory failure, and stridor have occurred. The temporal relationship of some gastrointestinal, cardiovascular and respiratory events to the administration of light was suggestive of mediastinal inflammation in some patients. Vision-related events of abnormal vision, diplopia, eye pain and photophobia have been reported.

Laboratory Abnormalities

PDT with PHOTOFRIN® may result in anemia due to tumor bleeding. No consistent effects were observed for other parameters.

OVERDOSAGE

PHOTOFRIN® Overdose

There is no information on overdosage situations involving PHOTOFRIN®. Effects of overdosage on the duration of photosensitivity are unknown. Laser treatment should not be given if an overdose of PHOTOFRIN® is administered. In the event of an overdose, patients should protect their eyes and skin from direct sunlight or bright indoor lights for 30 days. At this time, patients should test for residual photosensitivity (see PRECAUTIONS). PHOTOFRIN® is not dialyzable.

Overdose of Laser Light Following PHOTOFRIN® Injection

There is no information on overdose of laser light following PHOTOFRIN® injection in patients with esophageal carcinoma. Increased symptoms and damage to normal tissue might be expected following an overdose of light.

DOSAGE AND ADMINISTRATION

Photodynamic therapy with PHOTOFRIN® is a two-stage process requiring administration of both drug and light. Practitioners should be trained in the safe and efficacious treatment of esophageal cancer using photodynamic therapy with PHOTOFRIN® and associated light delivery devices. The first stage of PDT is the intravenous injection of PHOTOFRIN® at 2 mg/kg. Illumination with laser light 40–50 hours following injection with PHOTOFRIN® constitutes the second stage of therapy. A second laser light application may be given 96–120 hours after injection, preceded by gentle debridement of residual tumor (see Administration of Laser Light). In clinical studies, debridement via endoscopy was required 2 days after the initial light application.

See memo. → (attached)

Patients may receive a second course of PDT a minimum of 30 days after the initial therapy; up to three courses of PDT (each separated by a minimum of 30 days) can be given. Before each course of treatment, patients should be evaluated for the presence of a tracheoesophageal or bronchoesophageal fistula (see CONTRAINDICATIONS).

PHOTOFRIN® Administration

PHOTOFRIN® should be administered as a single slow intravenous injection over 3 to 5 minutes at 2 mg/kg body weight. Reconstitute each vial of PHOTOFRIN® with 31.8 mL of either 5% Dextrose Injection (USP) or 0.9% Sodium Chloride Injection (USP), resulting in a final concentration of 2.5 mg/mL. Shake well until dissolved. Do not mix PHOTOFRIN® with other drugs in the same solution. PHOTOFRIN®, reconstituted with 5% Dextrose Injection (USP) or with 0.9% Sodium Chloride Injection (USP), has a pH in the range of 7 to 8. PHOTOFRIN® has been formulated with an overage to deliver the 75 mg labeled quantity. The reconstituted product should be protected from bright light and used immediately. Reconstituted PHOTOFRIN® is an opaque solution, in which detection of particulate matter by visual inspection is extremely difficult. Reconstituted PHOTOFRIN®, however, like all parenteral drug products, should be inspected visually for

RE: DOSAGE AND ADMINISTRATION, Paragraph 1, last sentence:

More data are needed, before a sentence stating that "mandatory debridement may not be necessary..." can be included in PHOTOFRIN® labeling. The key clinical studies of PHOTOFRIN/PDT included mandatory debridement. Data must be submitted, detailing experiences with treatment of individual patients without debridement (and indicating that a substantial number of patients have been so treated, with satisfactory safety and effectiveness results).

If these data can be provided from existing records of patients who were treated without debridement, review of these data (and possibly inclusion of a statement in labeling that debridement may not be required) may be possible prior to, or in the early phases of, PHOTOFRIN marketing.

particulate matter and discoloration prior to administration whenever solution and container permit.

Precautions should be taken to prevent extravasation at the injection site. If extravasation occurs, care must be taken to protect the area from light. There is no known benefit from injecting the extravasation site with another substance.

Administration of Laser Light

Initiate 630 nm wavelength laser light delivery to the patient 40–50 hours following injection with PHOTOFRIN®. A second laser light treatment may be given as early as 96 hours or as late as 120 hours after the initial injection with PHOTOFRIN®. No further injection of PHOTOFRIN® should be given for such retreatment with laser light. Before providing a second laser light treatment, the residual tumor should be debrided. Vigorous debridement may cause tumor bleeding.

The laser system must be approved for delivery of a stable power output at a wavelength of 630 $\pm$3 nm. Light is delivered to the tumor by cylindrical OPTIGUIDE™ fiber optic diffusers passed through the operating channel of an endoscope. Instructions for use of the fiber optic and the selected laser system should be read carefully before use. Photoactivation of PHOTOFRIN® is controlled by the total light dose delivered. In the treatment of esophageal cancer, a light dose of 300 joules/cm of tumor length should be delivered. OPTIGUIDE™ cylindrical diffusers are available in several lengths. The choice of diffuser tip length depends on the length of the tumor. Diffuser length should be sized to avoid exposure of nonmalignant tissue to light and to prevent overlapping of previously treated malignant tissue. The total power output at the fiber tip is set to deliver the appropriate light dose using exposure times of 12 minutes and 30 seconds. Refer to the OPTIGUIDE™ instructions for use for complete instructions concerning the fiber optic diffuser.

HOW SUPPLIED

PHOTOFRIN® (~~sterile~~ porfimer sodium) for injection is supplied as a freeze-dried cake or powder as follows:

NDC XXXX-XXXX-XX – 75 mg vial

PHOTOFRIN® freeze-dried cake or powder should be stored at Controlled Room Temperature.

Distributed by

DIST. LOGO
[Name and address to be inserted when finalized]

Manufactured by

LEDERLE PARENTERALS, INC.
Carolina, Puerto Rico 00987

for

QLT LOGO

QLT PHOTOTHERAPEUTICS INC.
Seattle, WA 98101

Spills and Disposal

Spills of PHOTOFRIN® should be wiped up with a damp cloth. Skin and eye contact should be avoided due to the potential for photosensitivity reactions upon exposure to light; use of rubber gloves and eye protection is recommended. All contaminated materials should be disposed of in a polyethylene bag in a manner consistent with local regulations.

Accidental Exposure

PHOTOFRIN® is neither a primary ocular irritant nor a primary dermal irritant. However, because of its potential to induce photosensitivity, PHOTOFRIN® might be an eye and/or skin irritant in the presence of bright light. It is important to avoid contact with the eyes and skin during preparation and/or administration. As with therapeutic overdosage, any overexposed person must be protected from bright light.

CSO Review of LBLJ

CSO REVIEW OF LABELING

NDA: 20-451 for Photofrin December 13, 1995 amendment

The December 4, 1995 draft label was reviewed by the Medical, Chemistry, Pharmacology and Biopharm disciplines. Corresponding labeling comments were transmitted to the sponsor on December 4, 8 and 12, 1995. The December 13, 1995 submission provides draft labeling and includes the December 4, 1995 label with the changes requested in our December 4, 8 and 12, 1995 communications. The December 4, 1995 label has been amended as requested except for the following.

In the Clinical Studies subsection of the CLINICAL PHARMACOLOGY section, the sponsor noted the change from 14 to 13 in the following sentence. After one course of therapy, there was a statistically significant improvement in mean dysphagia grade (1.5 units, $p < 0.05$) and 13 of 17 patients could swallow liquids without difficulty 1 week and/or 1 month after treatment.

In the Pharmacokinetics subsection of the CLINICAL PHARMACOLOGY section, the following sentence was deleted as the third paragraph because it was duplicated and is included as the last sentence of the first paragraph.

> The influence of impaired hepatic function on PHOTOFRIN® disposition has not been evaluated.

In the WARNINGS section, the following sentence has been added as requested but uses the word avoid instead of limit.

> Following injection with PHOTOFRIN® precautions must be taken to avoid exposure of skin and eyes to direct sunlight or bright indoor light (see PRECAUTIONS).

In the PRECAUTIONS section, Information for patients subsection, the last sentence of the third paragraph is now a new paragraph

> Women of childbearing potential should practice an effective method of contraception during therapy (see Pregnancy).

in the ADVERSE REACTIONS section the statement in parentheses was added as follows.

> Photosensitivity reactions (mostly mild erythema on the face and hands) occurred in approximately 20% of patients treated with PHOTOFRIN®.

In the ADVERSE REACTIONS section the following was included but is now a separate paragraph.

> Most toxicities associated with this therapy are local effects seen in the region of illumination and occasionally in surrounding tissues. The local adverse reactions are characteristic of an inflammatory response induced by the photodynamic effect.

In the HOW SUPPLIED section and the vial and box label, the storage statement is the following and does not include "and protect from bright light" as requested.

> PHOTOFRIN® freeze-dried cake or powder should be stored at Controlled Room Temperature 15–30°C (59–86°F).

In the HOW SUPPLIED section, the reference to Lederle, who was originally going to distribute the product, has been removed. The new marketing partner will be added as distributor to the final printed copy.

In addition, the following requested changes were made.

We requested that a statement be added to the Clinical Studies subsection of the CLINICAL PHARMACOLOGY section to reflect that debridement was done as an integral part of the studies. The following statement was added.

> Debridement of residua was performed via endoscopy 96–120 hours after injection, after which any residual tumor could be retreated with a second laser light application at the same dose used for the initial treatment.

Regarding the ADVERSE REACTIONS section, we requested that adverse events occurring for less than 5% be put in paragraph form rather than a list. The following is the proposed paragraph.

> Serious and other notable adverse events observed in less than 5% of PDT-treated patients in the clinical studies include the following; their relationship to therapy is uncertain. In the gastrointestinal system, esophageal perforation, gastric ulcer, gastrointestinal hemorrhage, ileus, jaundice, and peritonitis have occurred. Sepsis has been reported occasionally. Cardiovascular events have included angina pectoris, bradycardia, cerebrovascular disorder, congestive heart failure, myocardial infarction, sick sinus syndrome, and supraventricular tachycardia. Respiratory events of bronchitis, bronchospasm, laryngotracheal edema, pneumonitis, pulmonary hemorrhage, pulmonary edema, respiratory failure, and stridor have occurred. The temporal relationship of some gastrointestinal, cardiovascular and respiratory events to the administration of light was

suggestive of mediastinal inflammation in some patients. Vision-related events of abnormal vision, diplopia, eye pain and photophobia have been reported.

In the DOSAGE AND ADMINISTRATION section, we requested that a statement concerning debridement from the Administration of Light subsection might be reworded and moved to the first paragraph of the DOSAGE AND ADMINISTRATION section. The sponsor include the following in the first paragraph of the DOSAGE AND ADMINISTRATION section.

> A second laser light application may be given 96-120 hours after injection, preceded by gentle debridement of residual tumor (see Administration of Laser Light). In clinical studies, debridement via endoscopy was required 2 days after the initial light application. However, experience has indicated that mandatory debridement may not be necessary due to natural sloughing action in the esophagus and may, in fact, needlessly traumatize the area.

RECOMMENDATIONS:

1. The respective Reviewers and Supervisors should review the changes as noted above for acceptability.

2. Reviewer and Supervisor signature below denotes that the sections of the December 13, 1995 amendment that pertain to their discipline are acceptable as draft labeling. Comments may be provided.

3. A separate review of the December 13, 1995 amendment may be provided.

Paul F. Zimmerman 12/17/95
Paul F. Zimmerman
Consumer Safety Officer

CSO REVIEW OF LABELING

NDA: 20-451 for Photofrin December 13, 1995 amendment

Yung-ao Hsieh 12-18-95
Yung Ao Hsieh, Ph.D., Chemistry Reviewer

Rebecca Wood 12-18-95
Rebecca Wood, Ph.D., Supervisory Chemist

cc:
Orig. NDA
Div File
HFD-150/PZimmerman
HFD-150/YHsieh
HFD-150/RWood
HFD-150/DMcGuinn
HFD-150/JDeGeorge
HFD-150/GWilliams
HFD-150/JRJohnson
HFD-426/ARahman

CSO REVIEW OF LABELING

NDA: 20-451 for Photofrin December 13, 1995 amendment

Dec 18, 1995
David McGuinn, Ph.D., Pharmacology Reviewer

Dec 18, 1995
Joseph DeGeorge, Ph.D., Supervisory Pharmacologist

cc:
Orig. NDA
Div File
HFD-150/PZimmerman
HFD-150/YHsieh
HFD-150/RWood
HFD-150/DMcGuinn
HFD-150/JDeGeorge
HFD-150/GWilliams
HFD-150/JRJohnson
HFD-426/ARahman

CSO REVIEW OF LABELING

NDA: 20-451 for Photofrin December 13, 1995 amendment

N.A.H. Atiqur Rahman 12/19/95
Atiqur Rahman, Ph.D., Biopharmaceutical Reviewer

Mehta 12/19/95
Mehul Mehta, Ph.D., Biopharmaceutical Supervisor

cc:
Orig. NDA
Div File
HFD-150/PZimmerman
HFD-150/YHsieh
HFD-150/RWood
HFD-150/DMcGuinn
HFD-150/JDeGeorge
HFD-150/GWilliams
HFD-150/JRJohnson
HFD-426/ARahman

Medical Officer Review of Revised Draft Labeling

NDA 20-451 **December 18, 1995**
Drug: Photofrin

Regarding: Photofrin draft labeling

Document Date 12-13-95

The following sentence is proposed in the Dosage and Administration section:

"However, experience has indicated that mandatory debridement may not be necessary due to natural sloughing action in the esophagus and , may, in fact, needlessly traumatize the area."

Reviewer comments:

I believe the statement is too dogmatic.

Recommended action:

1. The following statement should be substituted for that above:

"More recently, experienced investigators have indicated that mandatory debridement may not be necessary due to natural sloughing action in the esophagus, and may needlessly traumatize the area."

2. the sponsor must submit a list (by FAX transmission) of those experienced investigators that have been polled and that agree with this statement, since we have no data or literature backing it up. If possible they should obtain an estimate of the number of patients these investigators have treated by this method.

Grant A. Williams, MD

cc: NDA 20-451; HFD-150: PZimmerman, G Williams
DIVISION FILE John R Johnson, MD 12-18-95 faxed 12/19/95 PZ

Medical Officer Review of Revised Draft Labeling

NDA 20-451 **December 1, 1995**
Drug: Photofrin

Regarding: Fax Transmission to Photofrin labeling

Document Date of FAX: 11/28/95

The Applicant has agreed to many of the suggestions from a previous review, but has also made further changes to the proposed labeling.

1. PROPOSED CHANGE:

The response findings are altered to weigh the 1-week and 1-month response findings equally.

DISCUSSION

From the protocol description in MOR #2 it appears that the definition of objective response for this study did not include a specification that it be measured at a certain time; so I believe this change is legitimate.

REVIEWER RECOMMENDATIONS:

P. 4, next to last sentence put "some" before "palliation of their dysphagia."

P. 4-5: Delete "a statistically....difficulty." (This statement seems vague and is confusing to me.)

Insert: There was a statistically significant improvement in mean dysphagia grade (1.5; put p value here) and 14 of 17 treated patients could swallow liquids without difficulty 1 week and/or 1 month after treatment.

P 5 Line 9: Delete the clause "with minimal adverse reactions." (At least one patient in the overall group (pt. 2003) had a perforation which clearly is not a minimal reaction.) Move the clause "with minimal adverse reactions" to the end of the next sentence after "two or more grades of dysplasia." (This was the original placement of this clause in the NDA description of this group of patients.)

2. PROPOSED CHANGE

All references to photosensitivity are removed from the warning section and placed in the precautions section.

DISCUSSION

I disagree with the proposal to include no warning about photosensitivity. Ignorance of any precautions could lead to quite severe reactions, and a warning is appropriate.

RECOMMENDATION:

A statement such as the one now in the precautions section:

"Following injection with PHOTOFRIN, precautions must be taken to limit exposure of skin and eyes to direct sunlight or bright indoor lights, "

should be included in the warning section; it should reference the rest of the text which can be moved to the precautions section.

3. PROPOSED CHANGE

Clean up the adverse reactions section of events thought to be unrelated to PDT.

DISCUSSION

Regarding the proposal to clean up the list of adverse reactions, I am hesitant to undertake a process of retrospective exclusion; instead I propose:

RECOMMENDATIONS:

-Keeping the table intact that lists events occurring in 5% or more of patients.

-Of the other reactions, cite only those that were serious and do this in paragraph form rather than in a list.

4. PROPOSED CHANGE and DISCUSSION

Dosage and Administration:

This has 3 sections: an introductory paragraph, a Photofrin administration section and a section on administration of

Light.

The Applicant has taken the only reference to debridement (located in the laser light section) out of the labeling. Previously Ms. Mancini has expressed that at least some investigators believe that more harm than good is done by debridement and no longer do it. However, the fact is, we have no data on PDT of the esophagus done without debridement as the recommended followup procedure, and we have no data on safety or efficacy with this methodology.

RECOMMENDATION

-Move the sentence on debridement to the initial paragraph of the Dosage and Administration Section(if the Applicant wishes to move it from the laser light section). It might be reworded to state that 'debridement was done in the NDA studies'; and perhaps some reference could be made to there being some doubt that it was necessary.

-Furthermore, the clinical studies section needs to reflect that debridement was done as an integral part of these studies.

Recommended Action:

Send this review to the sponsor by FAX transmission for consideration. faxed 12/5/95 GAW

MD 12/1/95

Grant A. Williams, MD

John K Johnson, PhD 12-1-95

cc: NDA 20-451; HFD-150. PZimmerman, G Williams

Medical Officer Review of Information Relating to Draft Labeling

NDA 20-451 **December 22, 1995**
Drug: Photofrin

Regarding: Wording of the dosage and administration section of labeling; reference to debridement of tissue after initial treatment with PDT.

Document Date: **12-19-95 (FAX transmission)**

The following is from Medical Officer Review of Draft labeling from December 18, 1995:

"Recommended action:
1. The following statement should be substituted for that above:

"More recently, experienced investigators have indicated that mandatory debridement may not be necessary due to natural sloughing action in the esophagus, and may needlessly traumatize the area."

2. Prior to approval of final labeling, the sponsor should submit a list (by FAX transmission) of those experienced investigators that have been polled and that agree with this statement, since we have no data or literature backing it up. If possible they should obtain an estimate of the number cf patients these investigators have treated by this method."

The sponsor has responded with responses of 3 of the most experienced investigators:

Dr. Charles Lightdale, Columbia Presbyterian Hospital, NY

Dr. Norman Marcon, Wellesley Hospital in Toronto

Dr. Bergein Overholt, The Thompsons Cancer Survival Center in Knoxville Tn.

Collectively they have treated over 195 patients with photofrin and agree with the wording of the dosage and administration section as stated above.

Recommended Action
I recommend accepting the wording of the labeling as stated above.

Grant A. Williams, MD
cc: NDA 20-451; HFD-150: PZimmerman, G Williams, DW file
Robert J Detapp 12/22/95

Glaxo area #2

6.1.4 Efficacy analyses

6.1.4.1 Dysphagia analyses

Dysphagia data for the 19 patients is displayed individually in table 12A from the application (attached).

Reviewer comments:

I have made bold the 7/15 eligible (ie completely obstructed) patients who have an improvement in dysphagia grade at one month. As the sponsor indicates, one of these had a perforation.

As shown, 5 patients had a dysphagia grade improvement at both 1 week and one month. 2 others with improvement at one month had complications (perforation and stricture). Of the 5 responders that had Grade 5 dysphagia at baseline, 3 improved one grade and one each improved 2 grades and 3 grades. Of the 12 patients with Grade 5 dysphagia at baseline, 5 responded both at one week and at one month. 6/19 patients showed no evidence of improvement at either 1 week or one month.

Table 12A. Dysphagia Grade at Baseline, One Week and One Month for All Patients at First Course

Pt. No.	Baseline	One Week	One Month
	5	1[1]	4
	5	2[2]	4
	5	2[3]	4
	5	4[4]	2
	5	4[5]	3
	5	5*[6]	1*
	4	2[7]	2
	4	3** [8]	3**
	4	3[9]	4
	4	4	4
	5	2[10]	*ND*
	4	3[11]	ND
	5	3[12]	OS
	5	5	OS
	5	5[13]	OS
	4	2***[13]	ND
	4	4	OS
	5	OS	OS
	5	*OS*	*OS*

OS = Off-study
ND = Not done
* Dysphagia grade assessment rendered not evaluable; patient had esophageal perforation.
** Dysphagia grade assessment rendered not evaluable; patient had esophageal stricture.
*** Dysphagia grade assessment rendered not evaluable; patient received more than two laser sessions (three sessions).

From mic #2

6.1.4.2 Objective Response

Data on objective response is outlined in the sponsor's table 12G. 8 of the patients had a lumen visible at 1 month, though 3 of these had progressed compared to the one week assessment. The sponsor finds a response rate of 63% (12/19) at 1 week and 32% (6/19) at 1 month.

Table 12G. Smallest Luminal Diameter and Response Determinations at Baseline, One Week and One Month at First Course for All Enrolled Patients

Pt. No.	Baseline SLD* (cm)	One Week SLD* (cm)	One Week Response**	One Month SLD* (cm)	One Month Response**
	0.0	0.6	PR	not done	missing***
	0.0	not done	missing***	not done	missing***
	0.0	not done	missing	0.4	PR
	0.0	1.0	PR	1.0	PR
	0.2	0.8	PR	not done	missing
	0.0	1.2	PR	0.3	PD
	0.0	0.0	SD**	not done	missing***
	0.0	no tumor seen	CR3***	not done	missing
	0.3	0.7	PR[1]	not done	missing
	0.0	0.8	PR	1.0	PR
	0.9	not done	missing***	not done	missing***
	0.0	0.5	PR	not done	missing***
	0.0	0.8	PR	0.5	PR
	0.0	0.8	PR	0.2	PD
	0.3	0.3	SD	0.5	PR
	0.0	0.5	PR	1.5	PR
	0.0	1.0	PR	0.5	PD
	0.0	0.5	CR3	not done	missing
	0.0	0.5	PR	not done	missing***

* SLD = Smallest Luminal Diameter
** ACCO Response
*** Patient previously off-study
* Patient never treated
** Patient not evaluable due to invalid baseline measurement
*** Patient not evaluable due to protocol violation
1 Patient not evaluable due to pre-existing esophageal stricture

P. Zimmerm

NOV 14 1995

Medical Officer Review of Revised Draft Labeling

NDA 20-451 **October 30, 1995**
Drug: Photofrin

Regarding: Fax Transmission from Alexandra Mancini

Document Date of FAX: October 9, 1995

The sponsor has submitted proposed changes in the clinical studies section of the draft labeling.

The photofrin labeling is returning for a series of changes which will be leading to a final approval after chemistry issues are finalized in the near future. The Agency sent an approvable letter on July 13th which contained numerous changes in the original draft labeling which were to be contained in the final labeling. One of these was a comment originating from me removing any reference to statistical significance in efficacy results. This was agreed to.

Inclusion/Exclusion of efficacy data from ND:YAG

In reviewing the proposed changes to table 1 in the draft labeling, which lists results of the 236 patient study comparing outcome of YAG versus PDT in patients with partially obstructing disease, I have realized that the comparative data is not relevant to the indications approved and will leave the labeling quite vulnerable to misuse or mis-understanding. The following are points that support this contention:

-In MOR#1 the very poor data quality of all efficacy endpoints was noted; at most data points 30% of data was missing. It was determined that comparative evaluations of efficacy between PDT and YAG were not valid. In addition, no efficacy endpoint other than the dysphagia scale was felt to be intrinsically valid.

-The advisory committee did not approve the application for partially obstructed disease because of the lack of assurance of equivalence or superiority to YAG in efficacy and because of substantial local toxicity.

-According to my recollection, the decision to include the clause in the Indications Section about patients with partially obstructing disease who could not be treated with YAG, was based, not on subgroup analyses that convinced them of superiority of PDT (because such comparisons would be subject to the same data quality considerations) but upon the logical assumption that PDT would work in such patients if it worked in completely obstructed patients. In fact the idea for the phase IV study is based on the realization that we have NO data in this group since they were not eligible for either trial.

REVIEWER RECOMMENDATION:

Since the Approvable Indication does not include any patients treated in the randomized study of patients with partially obstructing esophageal cancer (Trial P19), efficacy data from this trial should not be included in the labeling.

DELINEATING GROUP WHERE LASER IS NOT INDICATED

The company has also proposed the following

"Analyses of objective tumor response by patient subsets showed that Photofrin(R)PDT may be superior to Nd:YAG for patients with narrow, angulated tumors such as found in the upper or lower third of the esophagus, and for those with small, flat tumors (less than 5 cm) or very long tumors (greater than 10 cm). Treating tumors in the upper third of the esophagus is difficult with the Nd:YAG laser because it is hard to maneuver the fiber tip in this narrow region. In lower-third lesions, angulation at the esophagogastric junction and technical problems associated with movement in this area (such as heart pulsations, respiratory movements, and swallowing contractions) make Nd:YAG treatments difficult. PDT is technically easier to administer in these regions. The advantage that PHOTOFRIN(R)PDT exhibits in treating small tumors is a reflections of PDT's ability to treat flat tumors because it is a diffuse, event treatment that does not use a thermal laser. With the Nd:YAG thermal laser, there is a risk of perforation when treating close to the esophageal wall. For this reasons, patients who have received prior therapy for esophageal cancer, particularly radiation therapy, which results in a flat fibrotic tumor morphology, may be more easily treated with Photofrin(R)PDT."

REVIEWER COMMENT

I consider such statements to be opinions supported at best by subset analyses of inadequate endpoints base on data of poor quality. Most seems to be conjecture.

REVIEWER RECOMMENDATION:

Patients in whom laser therapy was contra-indicated were not admitted to the comparative study; therefore subset analyses from this study are not relevant this determination. The issue of when laser therapy is contra-indicated relates to the use of a device and is not appropriate for inclusion in the labeling of this drug. No further qualification of the phrase "who, in the opinion of the physician, cannot be satisfactorily treated with Nd:YAG" would be appropriate.

Changes in Completely Obstructed Study:

In the proposed text the applicant needs to define response in this setting (PR: appearance of a visible lumen and CR: absence of tumor by endoscopy). The applicant proposes to note that 3

CR's occurred; however, the times of occurrence should also be noted since 2 were documented only at week 1. Again inclusion of week one data is proposed in addition to one month.

The new wording which includes time points other than the original response time of one month gives an inflated picture of benefit compared to the original wording for describing the results of this study. However, for a single arm study, I believe inclusion of efficacy data from multiple time points is legitimate, especially in a disease where there is no standard definition of response.

REVIEWER RECOMMENDATION:

In the study of completely obstructed disease, the applicant needs to define response in this setting (PR: appearance of a visible lumen and CR: absence of tumor by endoscopy). The applicant proposes to note that 3 CR's occurred; however, the times of occurrence should also be noted in the labeling since 2 were documented only at week 1.

Recommended Regulatory Action:

The following comments should be communicated to the applicant by FAX transmission after review by the Oncology Group Leader:

List of Comments to be Conveyed to Applicant:

1. Efficacy data from the randomized trial comparing PDT to ND:YAG laser therapy for the treatment of partially obstructing esophageal carcinoma (Protocol p-19) should not be included in the labeling for the following reasons:

   a. The Approvable Indication (complete obstruction or those who should not be treated with ND:YAG) does not include patients in the randomized study of partially obstructing esophageal cancer (Trial P19).

   b. The large amount of missing data on efficacy endpoints does not allow a valid comparison between arms.

   The sponsor is encouraged to publish the full study findings in the Oncology literature.

2. No further qualification of the phrase "who, in the opinion of the physician, cannot be satisfactorily treated with Nd:YAG" would be appropriate. Patients in whom laser therapy was contra-indicated were not admitted to the comparative study; therefore subset analyses from this study are not relevant this determination. The issue of when laser therapy is contra-indicated relates to the use of a device and is not appropriate for inclusion in the labeling of this drug.

3. In the study of completely obstructed disease, the applicant needs to define response in this setting (PR: appearance of a visible lumen and CR: absence of tumor by endoscopy). The applicant proposes to note that 3 CR's occurred; however, the times of occurrence should also be noted in the labeling since 2 were documented only at week 1.

4. Presentation of data from the study of complete obstruction by esophageal cancer on patients with a clinically important benefit from PDT is encouraged. The following are suggestions for this presentation:

   If information about the subset of patients with "a clinically important benefit from PDT" is included in the labeling, it should follow notation that this is a subset of patients of all treated, with the numerator , denominator, and percent of the treated population that it represents. The median should be included as a measure of the center of the data. The method of selecting those with benefit should be stated along with the methodology used for determining duration of benefit.

Grant A. Williams, MD

John R Johnson, MD 11-1-95

cc: NDA 20-451, HFD-150: PZimmerman, G Williams
Div File

include attached fax

agree Robert J Delap 11-14-95
acting Division Director

fax 11/16/95 FFE

3.0 Material Reviewed/Clinical Data Source

NDA 20-451: 164 volumes

Key Volume Numbers:

TOPIC	VOLUME
Labeling	1
Pharmtox	9
PK	28
Clinical	30-54
Study 73-19	33
Protocol	34
Patient Profiles	36-37
Listings	38-39
CRF Tabulations	100-102
CRFs	107-164
Study 73-20	40
Other studies	42
Summary of Efficacy	43
Summary of Safety	44
Integrated Summary	54
Literature	55-77

4.0 Important Dates

3-88	End of phase II meeting.
9-13-90	Meeting regarding interim analysis
10-8-92	Pre-NDA meeting
1-10-90	Lyophilized formulation amendment to protocol.

Study 019	Protocol	5/88		
9-88		amendments:	1	8/88
			2	8/88
7-92			3	3/89
			4	10/89
Study 020			5	10/90
4-89				
8-92				

5.0 Introductory comments:

This is a combination application for a drug and for a device. Part I of the application went to CDER, other parts of the application went to CDRH.

The drug and devices being evaluated are PHOTOFRIN® and OPTIGUIDE(TM) Fiber optic diffuser and specific lasers.

The following are pertinent points from the draft labeling submitted:

- **Indication** " for the reduction of obstruction and palliation of dysphagia in patients with completely or partially obstructing esophageal cancer."

- **Dose/route/schedule** -2 mg/kg of **photofrin** I.V. over 3 to 5 minutes, 40-50 hours prior to application of laser light.

  -300 joules per centimeter of tumor of **laser light**, at 630 +/- 3nm from a pumped dye laser through OPTIGUIDE fiber optic diffuser.

The claim is supported primarily on the by 2 studies in patients with esophageal cancer, P19 and P20.:

Clinical Studies:

P-19: Open label randomized study of pdt vs laser thermal ablation for partially obstructing esophageal cancer.

-Efficacy endpoints evaluated by the sponsor included palliation of dysphagia, time to palliation failure, objective tumor response, change in smallest luminal diameter.

-Formulation change occurred in January 1990, after about one third of the patients had been accrued to the P19 study.

P-20: -Open one-arm study of pdt for completely obstructing esophageal cancer.

Study	Arms of study	# pts. on PDT	# Pts. on YAG	# Investigative sites
p19	PDT vs ND:Yag	110	108	24 centers
p20	PDT	17		8 centers

Only the randomized study P-19 is reviewed in this Medical Officer Review #1. Review of Study P-20, studies in other tumor types, and safety overview will follow in MOR #2.

The following issues are not addressed in this review, but will be important to consider prior to the final approval decision:

- Impact of the manufacturing change which altered the ester/ether ratio.

If sufficient evidence exists to support the safety and efficacy of PDT as used in these trials, an evaluation will need to be made of how much of this evidence applies to the current formulation and drug. A formulation change was made (frozen to lyophilized) after accrual of about 1/3 of the patients in P19. Even later a major manufacturing change occurred leading to a difference in the ester/ether ratio of the drug substance.

- Completely obstructing esophageal cancer

Even if approval for partially obstructing esophageal cancer is not supported by study 019, approval might be sought for the indication of complete obstruction. This will be addressed in the near future, after review of study 020, in Medical Officer Review #2.

- Public health impact of off-label use of PDT

If PDT is approved for a very limited indication such as completely obstructing esophageal cancer, one must consider the safety implications of widespread off-label use in more benign settings such as in patients with skin cancer.

6.0 Clinical Studies

6.1 Trial P19

6.1.1 Review of Protocol P-19 (Review of 3/89 protocol):

Title: A RANDOMIZED, PHASE III COMPARATIVE STUDY OF THE SAFETY AND EFFICACY OF PHOTODYNAMIC THERAPY (PDT) UTILIZING PHOTOFRIN II (DIHEMATOPORPHYRIN ETHERS [DHE])

versus

THERMAL ABLATION THERAPY USING THE Nd:YAG LASER FOR PARTIALLY OBSTRUCTING ESOPHAGEAL CARCINOMA.

Design:

This was an open randomized study comparing PDT with photofrin and YAG laser therapy for patients with partially obstructing esophageal cancer. Stratification was by length of lesion (<10 cm vs ≥ 10 cm) and according to whether patients received prior therapy for esophageal cancer. Randomization within strata was balanced by center. Randomization was performed after baseline endoscopy.

Objective: To compare safety and efficacy of PDT with photofrin to that of thermal ablation in partially obstructing esophageal carcinoma.

Study Population:

The following were critical inclusion and exclusion criteria:

Inclusion Criteria:

Biopsy proven esophageal carcinoma stage T1-T3, any N, any M.

Pts. must be unwilling or unable to get radiation therapy or surgery.

Patients may have previously received other radiation, surgery, and/or chemotherapy.

Exclusion Criteria:

Patients could not have completely obstructing lesions (defined as inability to pass guidewire).

Patients were excluded for KPS<30.

Pts were excluded for inadequate organ function (Bilirubin>3, Creatinine >3, SCOT > 3Xnl, wbc < 2000, plt <50k, or PT >1.5).

Study Treatment:

PDT

- Photofrin II 2.0 mg/kg was given iv over 3-5 minutes.
- Laser light was to be administered 40-50 hrs later.
- Up to 3 courses of PDT were allowed, each 30 days apart.
- A maximum of 2 laser light treatments were allowed per course(injection) of photofrin.
- Light was administered at constant power output of 400 mw/cm diffusing tip and a treatment time of 12 minutes and 30 seconds.

2-3 days after laser light application, endoscopy was performed to remove necrotic tissue. Laser could be applied to residual tumor at this time. After a month, if dysphagia continued/recurred from tumor, patient could be retreated up to a maximum of 3 monthly treatments.

Light doses were described in the study report:

> "The light doses selected for use in this clinical trial were the lowest doses which consistently resulted in responses to PHOTOFRIN® treatment in patients with esophageal carcinoma, based on a survey of the PHOTOFRIN® medical literature[32,35]. As a result, a light dose of 100 J/cm^2 of tumor was selected for use with a microlens fiber while a dose of 300 J/cm of cylindrical diffuser was selected for use with a cylindrical diffuser fiber."

Regarding fiberoptics used in the study:

> "Participating centers were initially provided with an assortment of laser fibers from the five types available: one microlens and four lengths of cylindrical diffuser fibers (0.5, 1.0, 1.5, 2.0 and 2.5 cm lengths). Microlens fibers were used for surface illumination of tumors not greater than 0.5 cm in diameter and were labelled with the serial number prefix "ML". Cylindrical diffusing fibers could be used either intraluminally or interstitially due to the conical end."

Precautions for PDT therapy included preventing exposure to direct sunlight for 30 days after injection and draping the patient during transport to OR.

Nd:YAG

- Power: 15-90 watts

2-4 days after laser treatment, necrotic tumor was debrided. The goal of each session was to coagulate and remove entire tumor surface. No limits were placed on time or total energy needed to accomplish this. A course of laser therapy might consist of numerous applications, with endoscopy performed 4 days later to remove necrotic tumor.

Baseline Evaluation:

Baseline exam included the following:

- Esophagogram (for luminal diameter and tumor length).
- CT with and without contrast.

Followup:

Endoscopies were to be done monthly to evaluate response with videotape of session for 3 months then at 6 months. Followup tests to be done at 1wk, monthly X3 and 6 months included CBC, PT, SMAC-20, urinalysis, CXR, esophagogram, KPS, Dysphagia Grade, and endoscopy for assessment of efficacy and local toxicity (perforation, edema, mucositis). CT of Liver and esophagus were to be repeated at 3 months after completion of treatment.

The following were to be recorded at each endoscopy:

- Length
- Proximity to upper sphincter
- % circumference involved (maximum)
- Smallest diameter of lumen
- Consistency of tumor
- Location and dimensions of submucosal tumor
- Description of esophageal inflammation, mucositis, or perforation.
- Diameter and percent circumference of each 2cm interval involved by tumor.

Efficacy Considerations:

The following are the primary and secondary endpoints, and criteria for response as stated in the original protocol.

Primary

- Time to first recurrence (visual recurrence or progression).

- Symptom palliation (change in dysphagia grade) and duration.

Table 8A. Schedule of Evaluations: PDT vs Thermal Ablation With The Nd:YAG Laser*

	Baseline	Day 1 of Laser Therapy	Day 3-4	Day 5-8	One Week Post Laser Treatment	1 Mo.	2 Mo.	3 Mo.	6 Mo.
History and Physical Exam	X				X	X	X	X	X
ECG	X					X			
Endoscopy	X	X	X	X+	X	X	X	X	X
Esophagogram	X				X	X	X	X	X
Dysphagia Grade	X				X	X	X	X	X
Karnofsky Performance Status	X				X	X	X	X	X
Body Weight	X				X	X	X	X	X
CXR	X				X	X	X	X	X
CT Scan-Liver and Esophagus	X							X	
CBC	X				X	X	X	X	X
PT	X				X	X	X	X	X
SMAC-20**	X				X	X	X	X	X
Urinalysis	X				X	X	X	X	X
Adverse Experience Evaluation		X	X	X	X	X	X	X	X

* When the Nd:YAG laser treatment course is repeated or when a second or third course of PHOTOFRIN® is injected, procedures listed must be repeated, using the same schedule.

\+ Endoscopy for debridement of residual tissue after re-treatment

** SMAC-20 - Sodium, potassium, chloride, CO_2, LDH, glucose, BUN, creatinine, total protein, albumin, calcium, phosphorus, total bilirubin, direct bilirubin, SGOT, SGPT, CDH, alkaline phosphatase, uric acid, cholesterol and triglycerides.

Reference: Appendix I

- **Objective tumor response.**

Secondary:

KPS
Weight
Time to final treatment failure (termination due to progression, toxicity, death, or any reason related to treatment.
Survival

Response definitions:

CR

CR 1: Endoscopic and biopsy absence of tumor.

CR2: Endoscopic absence.

PR ≥50% decrease in tumor length and 50% decrease in product of length and width of tumor from proximal view in endoscope

or

≥50% increase in lumen diameter.

Stable disease

Progression:

Increase by 25% in tumor length and in product of length and width.
or
≥50% decrease of smallest luminal diameter after best response to therapy.
or
Reappearance after a CR.

Tumor response was to be confirmed in a blinded fashion by a panel using esophagograms and videotapes. Pts with stable disease and who remained symptomatic were to be removed from study after 2 full courses of PDT. With ND:Yag they were to continue until deemed futile.

Toxicity Considerations:

Laboratory test abnormalities were to be characterized by clinicians as to causality if either of the following applied:

-If the MD considered it clinically significant
-If the value fell outside 'Cyanamid Safety Limits'

All ADRs were to be reported according to a Cyanamid toxicity scale which is reproduced in the appendix of this review. Important highlights from this scale are abstracted below:

LFT:	≤1.25 X N*	Grade 0
	1.25-2.5 X N	Grade I
	2.5-5 X N	Grade II
	5-10 X N	Grade III
	>10 X N	Grade IV

Mucositis: III = Severe
IV= Very severe

Pulmonary: Grade II= exertional dyspnea
Grade III=Dyspnea at rest
Grade IV=Complete bed rest required.

Cutaneous:	I	Erythema
	II	dry desquamation, vesiculation, pruritis
	III	Moist desquamation, ulcers.
	IV	Exfoliative dermatitis.

Infection:	I	minor
	II	moderate
	III	major
	IV	with hypotension

Dysphagia Grade:	I.	Swallow solids without difficulty.
	II.	Able to swallow semisolids (blenderized food)
	III.	Able to swallow only liquids.
	IV.	Difficulty swallowing liquids.
	V.	Unable to swallow saliva.

Statistical Considerations:

The following analyses were anticipated:

- Incidence of side effects: Wilcoxon 2-tailed rank test
- Distribution of response to therapy Chi-Square Procedures
- 'Time to' :
  - -recurrence Kaplan-Meier estimates and Logrank Test
  - -tttf "

-response duration "
-Survival "

The study was designed to have 80% power to detect a hazard ratio of 1.5 in time to first treatment failure with 2-sided alpha = 0.05 if 199 events were observed. Total study duration was to be 18 months. 6 month followup was expected after the last patient was entered. Formal followup for all endpoints but survival was to be for 6 months.

6.1.2 Performance and Analysis methodology in P19

Number of Patients: 236 patients (230 planned)
First Randomized: 9-16-88
Last 7-16-92

Thirty-two clinical trial centers were initiated for this multicenter study, and twenty four of these centers randomized at least one patient. Within center and stratum, patients were allocated sequentially to treatment with either PDT or Nd:YAG therapy using a computerized randomization schema with a blocking factor of 4.

Breakdown of patient by center is shown in the Applicant's table 3A (not reproduced for this review). Distribution of pts by center appears balanced. Largest are Heier at Valhalla, NY, Marcon at Toronto, and Lightdale at Memorial.

The following paragraphs contain some of the details of therapy , as discussed by the applicant in the study report, which prevented standardization of some elements of treatment between the two arms

> "However, certain key elements of the therapy could not be standardized due to differences between laser devices used and differences in the use of the device by individual investigators. These elements included the type of laser light delivered (pulse versus continuous wave), the number of pulses of laser light delivered for each endoscopic laser session, the total number of Joules (J) delivered per laser session, and the total number of laser sessions per treatment course.
> The use of dilatation during any endoscopic procedure was not restricted. Dilatation could have been used to aid passage of the endoscope for laser treatment of distal tumor segments or as a therapeutic intervention. Investigators were asked to record the use of dilatation in the case report form, indicating the esophageal luminal diameters pre- and post-dilatation. Tumors that occupied less than 75% of the circumference of the esophageal lumen and that were not greater than 0.5 cm in length were treated with microlens-tipped optic fibers. It was necessary to debride at a separate endoscopy from the laser session in order to permit sufficient time for the

cytotoxic effect of PDT to occur. This is in contrast to Nd:YAG therapy where laser light application and debridement can occur during the same endoscopy. Thus, in Nd:YAG treated patients, a laser session may include debridement while for PDT patients, the debridement and laser procedures are separated."

"In summary, for a single course of PDT, the patient had to receive one injection of PHOTOFRIN®, and undergo up to two separate applications of laser light and two debridement sessions."

And regarding Yag:

"If the response to therapy was insufficient to palliate dysphagia, additional Nd:YAG laser sessions could be given at the investigator's discretion. Typically, therefore, one course of Nd:YAG laser therapy consisted of multiple laser therapy sessions. A course of Nd:YAG laser therapy ended when the investigator felt that the level of dysphagia palliation was sufficient, or that further application of the Nd:YAG laser was futile."

For Yag therapy, courses were described as follows:

a. The first laser session after an objective response evaluation of progressive disease was considered the start of a new treatment course.

b. All Nd:YAG laser sessions which were greater than 21 days from the previous laser session were considered the start of a new treatment course. This 21-day interval was considered to be sufficient time to allow regrowth of tumor.

Outcome data handling is described in the data conventions manual in Appendix III of the study report.

Within each course:

- Data collected on or within 17 days of treatment completion were considered Week 1.
- Data collected between 18 and 45 days after treatment completion were considered Month 1.

The following excerpt from the study report discusses changes made in final endpoints"

Table 3A Summary Of Patient Randomization By Treatment Group And Trial Site

TRIAL NO.	INVESTIGATOR	INSTITUTION	LOCATION	PATIENTS RANDOMIZED PDT	YAG	ALL
1	MCCAUGHAN	GRANT LASER CENTER	COLUMBUS,OH		7	15
2	PANISH/GRUNDFEST	CEDARS-SINAI MED. CENTER	LOS ANGELES, CA		3	4
3	PETRINI	SANSUM MEDICAL CENT./WILT	SANTA BARBARA, CA		0	0
4	JACOBS	MENORAH MEDICAL CENTER	KANSAS CITY, MO		5	9
5	HAYDEN	WASHINGTON UNIVERSITY	ST. LOUIS, MO		0	0
6	GOLDBERG	JEWISH HOSP. OF CINCINNATI	CINCINNATI, OH		2	3
7	BAKER+	PROVIDENCE MEDICAL CENTER	PORTLAND, OR		0	0
8	HEIER	WESTCHESTER MED. CENTER	VALHALLA, NY		21	44
9	MARCON	WELLESLEY HOSPITAL	TORONTO, ONTARIO		17	34
10	ECKHAUSER	CLEVELAND METRO GEN. HOSPITAL	CLEVELAND, OH		4	6
11	STIEGMANN	UNIV.OF COLORADO HLTH SCI. CENTER	DENVER, CO		7	14
12	BUCHI	UNIV. OF UTAH MEDICAL CENTER	SALT LAKE CITY, UT		1	2
13	PIETRAFITTA+	UNIV. HOSP. AT BOSTON MED. CENTER	BOSTON, MA		0	0
14	MIRHOSEINI	ST.LUKE'S HOSPITAL	MILWAUKEE, WI		0	3
15	SANFELIPPO+	MT.CARMEL MEDICAL CENTER	COLUMBUS, OH		0	0
16	FERGUSON	UNIV. OF CHICAGO HOSPITAL	CHICAGO, IL		0	1
17	NAVA	ROSWELL PARK MEM. INSTITUTE	BUFFALO, NY		7	15
18	BERNARD	UNIV. OF NORTH CAROLINA	CHAPEL HILL, N.C.		0	0
19	PINKAS	UNIV. OF SOUTH FLORIDA	TAMPA, FL		3	4
20	ROGERS/LOBRAICO	RAVENSWOOD HOSP./WENSKE LASER CENT.	CHICAGO, IL		0	1
21	LOCICERO	NORTHWESTERN MEMORIAL HOSP.	CHICAGO, IL		1	4
22	RICHARDS	VANDERBILT UNIVERSITY	NASHVILLE, TN		2	4
23	SIVAK	CLEVELAND CLINIC FOUNDATION	CLEVELAND, OH		4	8
24	LIGHTDALE	MEM. SLOAN KETTERING CAN. CENTER	NEW YORK, NY		12	21
25	SCHWEITZER	HENRY FORD HOSPITAL	DETROIT, MI		4	9
26	ZORN	UNIVERSITY OF ALABAMA	BIRMINGHAM, AL		0	3
27	SCHRIEBER/GARJIAN+	UNIVERSITY OF MARYLAND	BALTIMORE, MD		0	0
28	OVERHOLT	THOMPSON CANCER SURVIVAL CENTER	KNOXVILLE, TN		10	18
29	PIETRAFITTA	ABBOT NORTHWESTERN HOSPITAL	MINNEAPOLIS, MN		0	0
30	ALLEN	UNIV. OF CALIFORNIA, DAVIS MED CENT.	SACRAMENTO, CA		2	4
31	ARONCHICK	PENNSYLVANIA HOSPITAL	PHILADELPHIA, PA		5	9
32	LANZAFAME	ROCHESTER GENERAL HOSPITAL	ROCHESTER, NY		1	1
			TOTAL		118	236

+ Investigators initiated but subsequently withdrawn from the trial.

Reference: Appendix VII.A.

"Modifications were made to the protocol specified efficacy endpoints. A detailed discussion of these modifications is contained in Section 9.5. All modifications to the efficacy endpoints were made prior to the final analysis of the data.

These modifications were discussed with the FDA and agreed upon at an October 9, 1992 meeting, with subsequent correspondence. Pursuant to those discussions with the FDA, a post-hoc analysis of time to palliation (TPF) failure was performed."

A December 1992 memo is stated to have notified the FDA of the intent to do an analysis of time to palliation failure. They also state that the emphasis changed from proving superiority to proving equivalence with use of 95% confidence intervals.

Response

During the study it was noted that measurement of tumor was difficult and would not be likely to be helpful in response assessment. The smallest luminal diameter was felt to be better measure of response and this was the measurement used for determination of objective response in the analysis presented in the NDA.

Duration of response and Duration of palliation were not analyzed due to infrequent measurement of these endpoints.

TTF:

"Time to treatment failure (TTF) for the first course was calculated as the interval from randomization until the first possible evidence of lack of effect, recurrent dysphagia, progression of the primary tumor, toxicity, or death (see Section 8.2.4 for a detailed discussion)."

In more detail :

The post hoc time to *treatment failure* endpoint was defined as time to any of the following:

- Objective disease progression within esophageal lumen
- Worsening of dysphagia due to tumor
- Dilatation at 1 month or beyond for any reason
- Retreatment
- Termination due to treatment-related toxicities or complications

- **Death**
- Patient or investigator request for withdrawal
- Disease progression outside esophageal lumen and/or overall patient deterioration
- Therapeutic failure (failure to achieve a CR or PR)
- Protocol Violation (Restricted to violations that resulted in a significant deviation from Protocol specified delivery of therapy.)

Reviewer comments:

This is a very complex aggregate endpoint. In addition, many of the criteria seem vague. For instance, what degree of toxicity is sufficient?

Time to Palliation failure:

"Time to palliation failure was calculated as the interval from randomization until the first evidence of lack of symptom palliation, recurrent dysphagia (worsening of symptom grade from previous assessment), or toxicity (see Data Conventions). As opposed to time to treatment failure, death, unless treatment related, and disease progression were not considered reasons for failure."

In more detail:

For the post hoc *time to palliation failure endpoint* any of the following sufficed.

- Worsening dysphagia
- Failure to palliate
- Termination due to treatment-related toxicity or treatment-related death
- Dilatation
- Retreatment

Reviewer comments:

Some of these criteria are quite vague. Dilatation was allowed per protocol and not specified as an endpoint. What does failure to palliate mean?

The following excerpt from the sponsor's table summarizes the patient subsets used by the sponsor in various analyses:

	Number of Patients		
Patient Subset (Analysis)	PDT	Nd:YAG	Tot.
All randomized (Efficacy)	118	118	236
Treated (Safety)	110	108	218
Evaluable			
(Dysphagia - Week 1)	87	89	176
(Dysphagia - Month 1)	74	63	137
(Response - Week 1)	73	72	145
(Response - Month 1)	68	57	125

6.1.3 Results of Study P19

Eligibility

The sponsor's analysis was based on all patients randomized. On the sponsor's review of protocol eligibility when strictly applied, 8% on the PDT arm and 15% on the YAG arm were ineligible. The reasons for exclusion are extracted from table 10A:

	PDT	Nd:YAG	ALL
Reasons Ineligible			
Abnormal lab values*	5	7	12
Dysphagia Grade 1^	**2**	**4**	6
Radiation or chemo within 4 wks*	2	3	5
TE fistula prior to treatment	0	3	3
Candidate for Curative Surgery	0	1	1

Most of the violations of eligibility are not highly relevant to determining efficacy. The 9 patients in bold are ones I consider potentially important. 6 patients had only grade 1 dysphagia, 4 on YAG arm and 2 on PDT arm. It might be more difficult to show efficacy in such patients since

one would have to show absence of symptoms. 3 patients with TE fistula were on the YAG arm, and likely had a more poor prognosis.

As shown in the following excerpt from table 10b, 7 to 8% of the patients in each arm were not treated for various reasons. The following is in number of patients per arm:

Reasons Not Treated	PDT	Nd:YAG	All
Pt. Requests Withdrawal	**6**	2	8
TE fistula	0	3	3
Laser Malfunction	**2**	0	2
Nd:YAG Application Deemed Unsafe	0	2	2
Death	0	1	1
Disease Progression	0	1	1
Pt. a Candidate for Curative Surgery.	0	1	1

In bold you can see that 8 of the PDT patients and 5 YAG patients were not treated for reasons that do not seem disease-related, and hence could have been influenced by patient or investigator bias.

On page 92 of volume 1.33 the applicant states :

" A review of data indicated that the degree of variability in the timing of the efficacy assessments was similar for the two randomization groups.

Table 10C from the application reviews the number of patients with data available for dysphagia grading on followup:

Table 10C.
Summary Of Reasons Dysphagia Grades Were Not Available For First Course, By Visit

	Week 1				Month 1			
	PDT		Nd:YAG		PDT		Nd:YAG	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
No. Randomized	118	(100)	118	(100)	118	(100)	118	(100)
No. Treated	110	(93.2)	108	(91.5)	110	(93.2)	108	(91.5)
No. with Available Data	93	(78.8)	93	(78.8)	75	(63.6)	68	(57.6)
No. with No Available Data	25	(21.2)	25	(21.2)	43	(36.4)	50	(42.4)
Reasons Data Not Available								
On Study								
No. Eval. Performed	10		11		4		7	
Off Study								
Not Treated	8		10		8		10	
Death	2		2		14*		11*	
Other	5		2		17*		22*	

* Includes patients removed from study prior to the Week 1 assessment

About 20% of the patients in each arm had no followup data at week 1, and over 40% at the 1-month visit. The reasons seem symmetrically distributed between arms. However, the total of 39 patients with 'other' for the reason data was not collected at month 1 seems large. So overall, at one month, we have no repeat measurement on 43 (36%) of PDT patients and 50 (42%) of YAG patients. The percent onstudy but not evaluated is less than 10% in each group.

Table 10D in application (not reproduced) evaluates similar missing data for objective response.

The frequencies of patients in categories of 'not treated' and 'death' are balanced; whereas more YAG patients are classified as 'other.'
Overall, at one month, for objective luminal response we have no repeat measurement on 43

(36%) of PDT patients and 50 (42%) of YAG patients. The percent onstudy but not evaluated is about 5% in each group. The number offstudy prior to the one month measurement is 33% on the PDT arm and 36% on the YAG arm.

The following statement is made by the sponsor:

"For PDT patients in Course 1, available dysphagia data were considered evaluable (free of identified potentially confounding factors) for 94% (87/93) of observations during Week 1 and for 99% (74/75) of observations during Month 1. The corresponding figures for Nd:YAG patients were 96% (89/93) for Week 1 and 93% (63/68) for Month 1."

The sponsor noted that at baseline 5 photofrin and 2 YAG patients were considered inevaluable. At week 1, 6 PDT patients and 2 YAG patients were inevaluable (5 on PDT were for edema and 2 on YAG were for TE fistula). At 1 month, 1 PDT and 5 YAG patients with data were not evaluable (3 of the YAG were for fistula.

Randomization date was used as starting point for all time intervals. The sponsor notes that delay between randomization and treatment was similar on the 2 arms. Median delay was 3 days on each of the study arms. 80% were treated within 1 week. 12 /118 of PDT patients and 7/118 of ND:YAG randomized patients were assigned to incorrect strata by investigators.

Reviewer Comments:

Many of these minor irregularities would be of more concern if the comparative analysis between the arms showed a significant result, or if proof of superiority of PDT to YAG were absolutely critical to the application.

Table 10 G shows the distribution of starting times for therapy and supports the sponsor's assertion that the delays were balanced on the 2 arms.

Table10G
Summary of Time From Randomization to First Course* By Treatment Group

	PDT		Nd:YAG		ALL	
	No.	(%)	No.	(%)	No.	(%)
No. Randomized	118		118		236	
No. Treated	110	(100)	108	(100)	218	(100)
Interval from Randomization to First Course* (days)						
≤7	86	(78.2)	89	(82.4)	175	(80.3)
8-14	18	(16.4)	15	(13.9)	33	(15.1)
15-21	3	(2.7)	3	(2.8)	6	(2.8)
>21	3	(2.7)	1	(0.9)	4	(1.8)
Median (Range)	3		3		3	

* Start date of first course is date of PHOTOFRIN^{R} injection for PDT-treated patients or date of first laser treatment for Nd:YAG-treated patients.

In both treatment groups, approximately half the patients had not received prior therapy (50%, 59/118 PDT and 54%, 65/118 Nd:YAG), and most patients had tumors less than 10 cm in length (83%, 98/118 PDT and 81%, 95/118 Nd:YAG).

Due to the small number of patients in strata 3 and 4, the efficacy results were not analyzed by strata. Rather, the two stratifying variables were incorporated separately into the analyses.

The sponsor notes that similar numbers of courses were given in each arm. These data are summarized in table 10 I in the application (not reproduced for this review). So defined, the distribution of courses does seem similar on the 2 arms.

Reviewer Comments:

This whole concept of defining 'courses' seems artificial. Since a course is defined differently on each arm, it would be unclear to me what a difference between the arms would mean. Would a difference in treatment outcome per course be due to treatment or might it just be due to different definitions of 'course'?

Endoscopy and Debridement:

The sponsor's Table 10I.I (not reproduced) showed a comparison of compliance with endoscopy and possible debridement 2-4 days after laser treatment on the 2 arms. Compliance was less common in the laser arm (41% vs 72%). The sponsor notes the discrepancy on the YAG arm, however also notes that although it was protocol specified to do the endoscopy at 2-4 days it was not standard practice not to do such a followup endoscopy.

Patient disposition:

The sponsor's table 10J is reproduced from the submission and is worthy of careful scrutiny.:

Table 10J. Disposition Of All Patients By Treatment Group

	PDT		Nd:YAG		ALL	
	No.	(%)	No.	(%)	No.	(%)
No. Randomized	118	(100)	118	(100)	236	(100)
Study Status						
On Study	0	(0.0)	0	(0)	0	(0)
Off-Study	118	(100)	118	(100)	236	(100)
Death	37	(31.4)	25	(21.2)	62	(26.3)
Disease Progression	26	(22.0)	33	(28.0)	59	(25.0)
Inadequate Response/ Therapy Changed	5	(4.2)	11	(9.3)	16	(6.8)
Patient Request Withdrawal	20	(17.0)	19	(16.1)	39	(16.5)
AE Treatment Related	7	(5.9)	7	(5.9)	14	(5.9)
AE Non-Treatment Related	6	(5.1)	13*	(11.0)	19	(8.1)
Laser Problems	6	(5.1)	0	(0.0)	5	(2.1)
Protocol Complete	4	(3.4)	4	(3.4)	8	(3.4)
Protocol Violation*	1	(0.8)	1	(0.8)	2	(0.8)
Physician's Order	2	(1.7)	3	(2.5)	5	(2.1)
Lost to Follow-up	4	(3.4)	2	(1.7)	6	(2.5)
Alive 4	(3.4)	8	(6.8)	12	(5.1)	
Deceased	103	(87.3)	101	(85.6)	204	(86.4)
Lost to Follow-up	11	(9.3)	9	(7.6)	20	(8.5)

* Includes three patients: removed from study due to fistula formation prior to treatment.

* PDT Pt. No. received three laser applications during Courses 1 and 2

Nd:YAG Pt. No. received a laser application with a contact fiber

Reference: Appendices X.B , X.F

All patients were offstudy at the time of analysis. For the most part the reasons for going offstudy are balanced between the 2 arms. Slight imbalances include the occurrence of more PDT deaths onstudy (31% vs 21%). 9% of the patients were lost to followup for the survival analysis; only

5% were still known to be alive. The number going offstudy at patient request was high on both arms (17%). The fraction of patients going offstudy for death or progression was similar for the 2 arms: (53% on PDT and 49% on YAG); more went offstudy for death in the PDT arm and more went offstudy for progression on the YAG arm.

Reviewer Comments:

Given the variety of reasons for going offstudy, many of which seem poorly defined, time to offstudy is probably not a meaningful endpoint in this study.

Demographics:

The sponsor's table 10k shows demographics of the 2 arms:

Table 10K.Patient Pretreatment Characteristics For All Randomized Patients By Treatment Group

	PDT		Nd:YAG		ALL	
	No.	(%)	No.	(%)	No.	(%)
No. Randomized	118	(100)	118	(100)	236	(100)
Sex						
Male	89	(75.4)	80	(67.8)	169	(71.6)
Female	29	(24.6)	38	(32.2)	67	(28.4)
Age (years)						
<60	28	(23.7)	15	(12.7)	43	(18.2)
≥60	90	(76.3)	103	(87.3)	193	(81.8)
Median (Range)	68		72		70	
Race						
Caucasian	99	(83.9)	106	(89.8)	205	(86.9)
Black	15	(12.7)	8	(6.8)	23	(9.7)
Asian	3	(2.5)	0	(0.0)	3	(1.3)
Hispanic	1	(0.8)	4	(3.4)	5	(2.1)
Karnofsky Performance Status						
90-100%	45	(38.1)	34	(28.8)	79	(33.5)
70- 80%	52	(44.1)	56	(47.5)	108	(45.8)
50- 60%	17	(14.4)	23	(19.5)	40	(16.9)
30- 40%	4	(3.4)	5	(4.2)	9	(3.8)
Median (Range)	80		80		80	
Weight (kg)						
30-39	3	(2.5)	6	(5.1)	9	(3.8)
40-49	13	(11.0)	21	(17.8)	34	(14.4)
50-59	36	(30.5)	29	(24.6)	65	(27.5)
60-69	25	(21.2)	30	(25.4)	55	(23.3)
≥ 70	39	(33.0)	30	(25.4)	69	(29.3)
Missing	2	(1.7)	2	(1.7)	4	(1.7)
Median (Range)	62		60		61	

Reference: Appendix VII.A

72% of the patients were male and 28% female. Age less than 60 years was more frequent on the PDT arm (13% vs 24%). More patients were asymptomatic or had minimal symptoms at baseline

in the PDT arm.

Reviewer Comments:

Because of imbalances, age and performance status should be considered in any multivariate analysis of the most important endpoints.

Baseline dysphagia grades were similar as displayed in the sponsor's table 10 L:

Table 10L.Baseline Dysphagia Grade For All Randomized Patients By Treatment Group

	PDT		Nd:YAG		ALL	
	No.	(%)	No.	(%)	No.	(%)
No. Randomized	118	(100)	118	(100)	236	(100)
Dysphagia Grade						
1	2	(1.7)	4	(3.4)	6	(2.5)
2	52	(44.1)	49	(41.5)	101	(42.8)
3	28	(23.7)	23	(19.5)	51	(21.6)
4	32	(27.1)	40	(33.9)	72	(30.5)
5	4	(3.4)	2	(1.7)	6	(2.5)
Median	3		3		3	

18 patients in each arm had no baseline dysphagia grade recorded; the median dysphagia grade at entry was 3.

Baseline factors related to disease are displayed in the sponsor's table 10M:

Table 10M. Disease Presentation And Prior Therapy Usage/ Extent Of Disease Involvement At Baseline For All Randomized Patients By Treatment Group

	PDT		Nd:YAG		ALL	
	No.	(%)	No.	(%)	No.	(%)
No. Randomized	118	(100)	118	(100)	236	(100)
Disease Presentation at Randomization						
Pharynx	0	(0.0)	1	(0.8)	1	(0.4)
Gastric Carcinoma	5	(4.2)	4	(3.4)	9	(3.8)
Esophageal Carcinoma	113	(95.8)	113	(95.8)	226	(95.8)
Prior Therapy Usage/ Extent of Disease Involvement						
No Prior Therapy	63	(53.4)	67	(56.8)	130	(55.1)
Stage I	3	(2.5)	3	(2.5)	6	(2.5)
Stage II	22	(18.6)	13	(11.0)	35	(14.8)
Stage III	9	(7.6)	13	(11.0)	22	(9.3)
Stage IV	28	(23.7)	34	(28.8)	62	(26.3)
Unknown	1	(0.8)	4	(3.4)	5	(2.1)
Prior Therapy	55	(46.6)	51	(43.2)	106	(44.9)
M0	28	(23.7)	31	(26.3)	59	(25.0)
M1	26	(22.0)	18	(15.3)	44	(18.6)
Unknown	1	(0.8)	2	(1.7)	3	(1.3)

96% of the patients had esophageal cancer as specified. About half had received prior therapy. Distribution of patients among tumor stages was relatively similar on the 2 arms.

Location of baseline tumor is shown in the sponsor's table 10 O:

Table 10O.
Baseline Histology And Tumor Size And Location For All Randomized Patients By Treatment Group

	PDT		Nd:YAG		ALL	
	No.	(%)	No.	(%)	No.	(%)
No. Randomized	118	(100.0)	118	(100.0)	236	(100.0)
Histology						
Adenocarcinoma	62	(52.5)	59	(50.0)	121	(51.2)
Esophagus	57	(48.3)	55	(46.6)	112	(47.5)
Stomach	5	(4.2)	4	(3.4)	9	(3.8)
Squamous Cell	54	(45.8)	59	(50.0)	113	(47.9)
Other	2	(1.7)	0	(0.0)	2	(0.8)
Location in Esophagus*						
Upper 1/3	23	(19.5)	29	(24.6)	52	(22.0)
Middle 1/3	47	(39.8)	49	(41.5)	96	(40.7)
Lower 1/3	44	(37.3)	37	(31.4)	81	(34.3)
Unknown	4	(3.4)	3	(2.5)	7	(3.0)
Length (cm)**						
< 10 cm tumor	98	(83.1)	96	(81.4)	194	(82.2)
≤ 5	55	(46.6)	67	(56.8)	122	(51.7)
6-9	43	(36.4)	29	(24.6)	72	(30.5)
≥ 10 cm tumor	16	(13.6)	18	(15.3)	34	(14.4)
Missing	4	(3.4)	4	(3.4)	8	(3.4)

* Tumor location was based on the proximal tumor margin.
** Tumor length was based on both proximal and distal tumor margins.

About 60% of the lesions were adenocarcinoma; distribution of tumors along the axis of the esophagus and sizes lengths of lesions were relatively similar on the 2 arms. About 4% of the patients had gastric rather than esophageal cancer.

Reviewer Comments:

The high incidence of adenocarcinoma is consistent with recent epidemiologic findings.

As shown in the sponsor's table 10 P (not reproduced for the review), circumferential involvement and luminal diameter were similarly distributed on the 2 arms. Three fourths of the patients had involvement of at least 75% of the esophageal circumference. About half had luminal diameter less than or equal to 0.5 cm.

Therapy delivered

The sponsor's table 11A outlines the delivery of photofrin to the PDT arm:

Table11A. Dose Of PHOTOFRIN® At First Course For PDT-Treated Group

	No.	(%)
No. Randomized	118	
No. Treated	110	(100)
Dose (mg/kg)*		
≤1.80	1	(0.9)
1.81 - 1.90	5	(4.5)
1.91 - 2.00	76	(69.1)
2.01 - 2.10	23	(20.9)
2.11 - 2.20	4	(3.6)
> 2.20	1	(0.9)
Preparation of PHOTOFRIN®		
Frozen	43	(39.1)
Lyophilized**	67	(60.9)

* As calculated by total mg dose given and baseline weight.
** Date of first patient treated with lyophilized = January 6, 1990.

8 patients (7%) never received photofrin. Of the 110 patients receiving photofrin, 90% received the planned dose of 2.0 mg/kg +/- 5%. This would appear adequate since we have little evidence of a steep dose response curve with PDT. 67 patients, or 61%, received the lyophilized formulation which is being considered in this NDA.

Reviewer comments:

Not only was there a change in formulation from Frozen to Lyophilized during this study, toward the end of this study there was a change in manufacturing process which resulted in a change in ratio of ester to ether linkages in the drug substance.

Lasers used were all continuous Argon ion pumped dye lasers (table 11B, not reproduced). The protocol called for application of light between 40 to 50 hours after photofrin for the first treatment and between 96 to 120 hour for the second treatment.

Compliance with these guidelines is outlined in table 11C from the sponsor's application:

Table 11C. Interval From Injection To First And Second Laser Application At First Course For PDT-Treated Group

	No.	(%)
No. Randomized	118	
No. Treated with First Laser Light Application	110	(100)
Interval From Injection to First Light Application (hrs)		
<40	2	(1.8)
40 - 50	87	(79.1)
>50	20	(18.2)
Missing	1	(0.9)
Median (Range)	46	
No. Treated with Second Laser Light Application	53	(100)
Interval From Injection to Second Light Application (hrs)		
<96	24	(45.3)
96 - 120	23	(43.4)
>120	6	(11.3)
Median (Range)	97	

During the first application of light to 110 patients, about 20 % of patients were treated late; about half the patients underwent a second light treatment, and of these 24 (45%) received light earlier than the specified 96 hours.

Reviewer Comments:

As this table demonstrates, there was considerable heterogeneity in timing of light delivery; most notably that half of the patients received 2 light applications. Important factors to consider in analyzing safety and efficacy will be which formulation the patients received and tne number of light courses that the patients received. Certainly the latter analysis could be fraught with associated bias (bigger mors getting more treatment, healthier patients getting a second treatment).

The sponsor did a nice presentation of number of light treatments versus the tumor parameters of length, location, luminal diameter, and % circumferential involvement in table 11 D (table not reproduced in this review). There was no obvious correlation between number of courses (one or two) and any of these parameters.

The number of YAG laser applications at first course is outlined by tumor parameters in the sponsor's table 11E:

Table11E.
Baseline Tumor Characteristics By Number Of Laser Applications At First Course For Nd:YAG-Treated Group

	No. With Characteristic No. (%)	One Laser Application Only No. (%)	Two Lasers Applications Only No. (%)	≥ Three Laser Applications No. (%)
No. Treated	108 (100)	28 (100)	40 (100)	40 (100)
Tumor Length*(cm)				
≤ 5	66 (61.1)	21 (75.0)	24 (60.0)	21 (52.5)
6 - 9	27 (25.0)	4 (14.3)	8 (20.0)	15 (37.5)
≥ 10	14 (13.0)	2 (7.1)	8 (20.0)	4 (10.0)
Missing	1 (0.9)	1 (3.6)	0 (0.0)	0 (0.0)
Location within the Esophagus				
Upper 1/3	26 (24.1)	8 (28.6)	9 (22.5)	9 (22.5)
Middle 1/3	45 (41.7)	12 (42.9)	19 (47.5)	14 (35.0)
Lower 1/3	36 (33.3)	7 (25.0)	12 (30.0)	17 (42.5)
Missing	1 (0.9)	1 (3.6)	0 (0.0)	0 (0.0)
Smallest Luminal Diameter (cm)*				
≤ 0.50	53 (49.1)	15 (53.6)	22 (55.0)	16 (40.0)
0.51-0.75	15 (13.9)	3 (10.7)	5 (12.5)	7 (17.5)
0.76-1.00	27 (25.0)	7 (25.0)	9 (22.5)	11 (27.5)
> 1.00	10 (9.3)	2 (7.1)	3 (7.5)	5 (12.5)
Unknown	3 (2.8)	1 (3.6)	1 (2.5)	1 (2.5)
% Circumferential Involvement*				
< 75	21 (19.4)	9 (32.1)	3 (7.5)	9 (22.5)
≥ 75	86 (79.6)	19 (67.9)	36 (90.0)	31 (77.5)
Unknown	1 (0.9)	0 (0.0)	1 (2.5)	0 (0.0)

* At baseline endoscopy.

Of the 108 treated patients, 28 (26%) received one laser application, 40 (37%) received exactly 2 applications, and 40 (37%) received 3 or more applications. There is no clear correlation between number of treatments and tumor parameters. Laser failure limited the amount of laser treatment given to 5 PDT patients and 1 YAG patient. All but one (patient , occurred at a second or subsequent application rather than at first application. Over 90% of the laser applications for PDT

were delivered without interruption. Most interruptions were due to problems with laser or fiber-optics.

The reasons for terminating the YAG laser therapy sessions is instructive as outlined in the sponsor's table 11h:

Table 11H.
Summary Of Reasons For Termination Of Laser Application At First Course For Nd:YAG-Treated Group

Application	1st Laser Application		2nd Laser Application		3rd Laser Application		≥4th Laser	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
No. Treated	108	(100)	78	(100)	37	(100)	38	(100)
Reasons for Termination of Laser Application								
Sufficient Treatment Given	91	(84.3)	71	(91.0)	33	(89.2)	32	(84.2)
Adverse Experiences	12	(11.1)	6	(7.7)	4	(10.8)	4	(10.5)
Pt. Intolerance	8		4		3		1	
Tumor Bleeds	2		0		1		3	
Edema	2		0		0		0	
Cardiac Problems	0		2		0		0	
Technical Problems	5	(4.6)	1	(1.3)	0	(0.0)	2	(5.3)
Powermeter/Laser	3		0		0		2	
Other	2		1		0		0	

About 90% of sessions were stopped because sufficient treatment was given; most of the other 10% were stopped because of patient intolerance.

Reviewer Comments:

Only 1 PDT patient stopped therapy because of 'medical problems.' These data would suggest that for the light application session, the YAG sessions cause more patient discomfort.

The number of endoscopies performed for the first course is listed in the sponsor's table 11 I:

Table11I.
Number Of Endoscopies Performed During The First Course By Treatment Group

	PDT No. (%)	Nd:YAG No. (%)
No. of Patients Treated	110 (100)	108 (100)
No. of Endoscopies		
1	11 (10.0)	14 (13.0)
2	62 (56.4)	37 (34.3)
3	35 (31.8)	32 (29.6)
4	2 (1.8)	16 (14.8)
≥5	0 (0.0)	9 (8.3)

From this we see that the median number of endoscopies was 2 on each arm, but that the occurrence of 4 or more endoscopies per `course' was more common on the Nd:YAG arm.

Reviewer Comments:

We must remember that the definition of `course' for nd:YAG is retrospective and somewhat arbitrary. Of more relevance to the patient would be :
-number of endoscopies per unit time, perhaps in first month.
-morbidity of each endoscopy.
-time without an endoscopy.

Table 11J from the application explores total number of endoscopies on the 2 arms:

Table11J.
Distribution Of Endoscopic Treatment Procedures During The First Course By Treatment Group

	PDT No. (%)	Nd:YAG No. (%)
Total Endoscopies	248 (100)	307 (100)
Laser Application Only	129 (52.0)	206 (67.1)
Debridement Only	66 (26.6)	42 (13.7)
Combination (Laser and Debridement)	35 (14.1)	58 (18.9)
Assessment	18 (7.3)	1 (0.3)

This shows that about 75% of the endoscopies included laser treatment on the Nd:YAG arm versus 50% on the PDT arm. About 40% of the endoscopies on the PDT arm included debridement.

Table 11k from the application demonstrates duration of therapy for course 1:

Table 11K.Duration Of Treatment* At First Course By Treatment Group

	PDT		Nd:YAG	
	No.	(%)	No.	(%)
No. Randomized	118		118	
No. Treated	110	(100)	108	(100)
Duration (days)				
≤3	11	(10.0)	27	(25.0)
4 - 6	54	(49.1)	25	(23.1)
7 - 10	37	(33.6)	23	(21.3)
> 10	8	(7.3)	33	(30.6)
Median	6		7	

* From injection (PDT) or first laser (Nd:YAG) until last laser or debridement endoscopy.

50% of the patients Nd:YAG patients and 60% of PDT patients were finished with treatment in less than one week, when duration of treatment is measured from first therapeutic intervention to last endoscopy. More YAG patients were treated over a duration of more than 10 days: (33% vs 8%).

Reviewer Comments:

This information for each group is of interest, however, comparisons are of unclear value since the meaning of a 'course' of therapy differs for the 2 arms.

6.1.4 Efficacy Analyses

6.1.4.1 Dysphagia Grade:

- **Applicant's Analysis**

Results from the sponsor's analysis of dysphagia are reproduced from table 12A:

Table
12A. Change From Baseline in Dysphagia Grade Over Time at First Course by Treatment Group

	All Available Grades			
	PDT		Nd:YAG	
VISIT	NO. PTS.	AVG. SCORE	NO. PTS.	AVG. SCORE
Baseline	118	2.86	118	2.89
Week 1	93	2.22	93	1.98
Change	93	-0.73	93	-0.90
95% C.I.				
Within Grp.[1]		(-0.98, -0.48)		(-1.13, -0.67)
Between Grp.[2]		0.17 (-0.17, 0.51)		
Month 1	75	2.09	68	2.18
Change	75	-0.75	68	-0.68
95% C.I.				
Within Grp.[1]		(-1.02, -0.48)		(-0.93, -0.42)
Between Grp.[2]		-0.07 (-0.45, 0.31)		
Month 2	28	2.61	20	2.30
Change	28	-0.11	20	-0.40
Month 3	12	2.25	8	2.38
Change	12	0.00	8	0.13
Month 6	5	2.20	4	1.50
Change	5	-0.20	4	-0.25

1. 95% C.I. for within group mean change from baseline.
2. 95% C.I. for between g

The fraction of randomized patients with data on this endpoint at 1 week, 1 month and 2 months was 79% (186/236), 61% (143/236), and 20% (48/236) respectively.

There are 2 questions of special interest:

- **Within arm, did therapy appear to confer benefit?**
- **Was there a clinically and statistically significant difference between the arms?**

Reviewer Comments:

For the considering whether benefit was realized there are 2 major issues. First, would there have been a placebo effect associated with being onstudy; ie would dysphagia grade have improved with placebo? Second, is the observed effect clinically significant; ie what is the meaning of a given change in dysphagia grade in a given situation.

The relevant data is extracted from this table in a simplified form below

Mean Dysphagia Grades at 1 wk and 1 month:

	PDT	YAG
Baseline	2.86	2.89
Week 1	2.22	1.98
Month 1	2.09	2.18

For the PDT arm changes from baseline of mean grade were -.64 and -.77 at one week and one month respectively. For YAG the changes were -.92 and -.71 respectively.

As shown in the sponsor's calculations, no significant difference was seen between arms. However, within each arm, changes from baseline were statistically significant at both time points since the 95% ci of differences from baseline do not overlap zero.

The sponsor also did an evaluation of 'evaluable patients' including 87 PDT patients and 89 YAG patients at week 1. Results were similar to the inclusive analysis.

The sponsor also categorized numbers of patients with improvement at 1 week and at one month in table 12B:

Table12B Summary of Improvements From Baseline in Dysphagia Grade at Week 1 and Month 1 Visits by Treatment Group

	All Available Grades			
	PDT		Nd:YAG	
	NO. PTS.	(%)	NO. PTS.	(%)
Randomized	118	100.0	118	100.0
Improved* at Week 1 and Month 1	28	23.7	27	22.9
Improved* at Week 1 Only	24	20.3	30	25.4
Month 1 Missing	12		18	
Month 1 Not Improved	12		12	
Improved* at Month 1 Only	13	11.0	7	5.9
Week 1 Missing	4		3	
Week 1 Not Improved	9		4	
No Evidence of Improvement+	38	32.2	35	29.7
Month 1 and Week 1 Not Improved	16		19	
One Visit Not Improved, 1 Missing	22		16	
Both Week 1 and Month 1 Missing	15	12.7	19	16.1

* at least one dysphagia assessment (Week 1 or Month 1) taken
\+ Improvement with respect to baseline dysphagia grade

From this we see that 24% of the PDT arm had an improved score at 1 week and 1 month. About a third of the patients on each arm with followup had no evidence of improvement; 13% had no followup evidence.

Reviewer Comments:

This analysis is slanted toward improvement since it considers improvement but not deterioration. Test variation alone would lead to an equal number improving and worsening, whereas treatment effect would be expected to yield an excess number improving over the number worsening.

Table 12C (attached) gives the details of number of patients on each arm with improvement, no improvement, or missing data at week 1 and month 1.

Despite the missing data, it would appear to me that more than half the patients with higher grade dysphagia on the **PDT arm** showed improvement at 1 wk and/or 1 month :

Baseline Grade	# at baseline	# Improved at 1 wk	# Improved at 1 mo
1	2	1	1
2	52	9	11
3	28	17	10
4	32	24	19
5	4	2	1
1 and 2	54	10	12
3 to 5	64	41	30

The results with **Nd:YAG laser arm** are qualitatively similar to those with PDT as shown by similar display of this data:

Baseline Grade	# at baseline	# Improved at 1 wk	# Improved at 1 mo
1	4	0	0
2	49	16	7
3	23	13	7
4	40	26	20
5	2	2	1
1 and 2	53	16	7
3 to 5	65	40	28

Table 12C. Summary of Improvement From Baseline in Dysphagia Grade at Week 1 and Month 1 Visits by Baseline Dysphagia Grade and Treatment Group

Baseline Dysphagia Grade TOTAL PTS.	Improved				Not Improved		Missing	
	PDT No. (%)	Nd:YAG No. (%)	PDT No. (%)	Nd:YAG No. (%)	PDT No. (%)	Nd:YAG No. (%)	PDT No. (%)	Nd:YAG No. (%)
Week 1								
1	2 (100)	4 (100)	+0 (0%)	+0 (0%)	1 (50%)	4 100%)	1 (50%)	0 (0%)
2	52 (100)	49 (100)	9 17%)	16 (33%)	29 (56%)	22 (45%)	14 (27%)	11 (22%)
3	28 (100)	23 (100)	17 (61%)	13 (57%)	6 (21%)	5 (22%)	5 (18%)	5 (22%)
4	32 (100)	40 (100)	24 (75%)	26 (65%)	3 (9%)	5 (13%)	5 (16%)	9 (23%)
5	4 (100)	2 (100)	2 (50%)	2 (100%)	2 (50%)	0 (0%)	0 (0%)	0 (0%)
Month 1								
1	2 (100)	4 (100)	+0 (0%)	+0 (0%)	1 (50%)	4 (100%)	1 (50%)	0 (0%)
2	52 (100)	49 (100)	11 (21%)	7 (14%)	22 (42%)	20 (41%)	19 (37%)	22 (45%)
3	28 (100)	23 (100)	10 (36%)	7 (30%)	9 (32%)	5 (22%)	9 (32%)	11 (48%)
4	32 (100)	40 (100)	19 (59%)	20 (50%)	2 (6%)	5 (13%)	11 (34%)	15 (38%)
5	4 (100)	2 (100)	1 (25%)	0 (0%)	0 (0%)	0 (0%)	3 (75%)	2 (100%)

+Patients within a baseline dysphagia grade of 1 cannot show improvement

Reference: Appendices IV, IX.A, IX.B

PHOTOF 9401700:T2 (M11/AM4-2)
03/15/94

On pp 142 to 147 of volume 1.33, the sponsor does a detailed subgroup analysis of dysphagia grade versus tumor size and tumor position. More benefit was apparent with tumors of the middle esophagus and less for proximal tumors. In general the data pattern was not obviously different for PDT versus YAG. Similarly results were similar in the 106 patients who had received prior therapy as in the 130 patients with no prior therapy. Results in the 75 patients from smaller sites were similar to results in the 161 patients at the seven 'larger sites' (defined as a site enrolling 14 or more patients).

The sponsor displays the data for the 7 larger sites on p 151 of Volume 1.33. Site 1, site 17, site 24 favored PDT whereas sites 11, 28, and smaller sites favored YAG. None of the differences appear to be inconsistent with random variation.

Time to treatment failure:

in the protocol 'time to final treatment failure' was a secondary endpoint and was to be time from randomization until "termination of patient from the study due to : disease progression, unacceptable toxicity, death, or any reason related to treatment such as patient or investigator request."

The sponsor's assessment of reasons for going offstudy is given in table 12 I from the application:

Table 12I. Summary of Time to Treatment Failure For All Patients by Treatment

	PDT		Nd:YAG	
	NO. PTS.	(%)	No. PTS.	(%)
Randomized	118	100.0	118	100.0
Number Failures/Reason	110	93.2	111	94.1
Progressive disease	20		23	
Worsening dysphagia	26		22	
Dilatation	16		10	
Retreatment	9		10	
Treatment-related term	6		5	
Death (any cause)	18		11	
Pt. request/Pt. failure	10		17	
Patient deterioration	5		13	
Number Censored/Reason	8	6.8	7	5.9
Non-treatment related term.	8		7	
Median TTF (days) [95% CI]	35 [34, 40]		40 [33, 42]	
Range	(0-211)		(0-183)	
Wilcoxon Chi-square (1 df)/**p-value**	0.008/**0.9268**			
Mantel-Cox Chi-square (1 df)/p-value	0.012/0.9140			
Hazard Ratio (Nd:YAG/PDT)*	0.99			
[95% CI]	[0.76, 1.29]			

* BMDP2L with Treatment variable as covariate.

Only 7 or 8 patients are censored in this analysis. Kaplan-Meier plots are identical. Median TTF was 35 days on the PDT arm and 40 days on the YAG arm, and there was no significant difference in the 2 arms (p=0.91).

Reviewer Comments:

95% confidence intervals are not really important since this endpoint is rather vague.

Time to palliation failure

This retrospective endpoint was time from randomization until first evidence of : worsening dysphagia, treatment related toxicity, failure to palliate, retreatment or dilation after 1 week.

Reviewer Comments:

This endpoint seems intolerably vague. For instance, both treatments have some inherent treatment-related toxicity, so how much toxicity is needed to trigger this endpoint. How do you define failure to palliate and when? Retreatment or lumenal dilation might have been done routinely rather than at the sign of failure.

The details of the analysis from the sponsor's table 12 J are of interest:

Table12J.
Summary of Time to Palliation Failure for All Randomized Patients in First Course by Treatment Group

	TREATMENT			
	PDT		Nd:YAG	
	No.	(%)	No.	(%)
Number Randomized: 236	118	(100)	118	(100)
Number Failures/Reason	94	(79.7)	83	(70.3)
Worsening dysphagia at 1 Week	10		4	
Worsening dysphagia at > Week 1	31		31	
Failure to palliate	28		29	
Termination - treatment related	5		5	
Death - treatment related	0		0	
Dilatation or retreatment > Week 1	20		14	
Number Censored/Reason	24	(20.3)	35	(29.7)
Censored reason (non-failures)	24		35	
Median TPF (days)[95% CI]*	34	[31,37]	42	[33,45]
Range		(0-211)		(0-183)
Wilcoxon Chi-square (1 df) /p-value		2.769 / **0.0961**		
Mantel-Cox Chi-square (1 df) /p-value		1.889 / **0.1694**		
Hazard Ratio (Nd:YAG/PDT)°		**0.82**		
95% C.I.		**[0.60, 1.10]**		

a: Brookmyer - Crowly Method.
b: A Cox regression model with one term for treatment was used to calculate these estimates. This regression analysis was generated via SAS using PROC BMDP2L.

I have highlighted minor differences and nonsignificant p values for comparisons on the 2 arms. 24 to 35 patients per arm were censored in this analysis.

Reviewer Analysis of Dysphagia data:

An analysis of the primary electronic data was performed using Access (database manager) and Excel (spreadsheet) software.

The distribution of baseline dysphagia data according to reviewer analysis of data is outlined in the following table. In the middle and right columns are number of responders at one month and per cent response grouped according to baseline grade.

1 mo. Dysphagia Response*, Distribution of patients by Baseline Grade

	#Patients at baseline		# Responders*		Response*	
Baseline Grade	PDT	YAG	PDT	Yag	PDT	YAG
	5					
1	2	4			0%	0%
2	48	49	9	9	19%	18%
3	27	23	10	7	37%	30%
4	32	40	20	19	63%	48%
5	4	2	1		25%	0%
Total	118	118	40	35	34%	30%

*Response defined as change of at least one dysphagia grade from baseline.

From this it is obvious that response rates were higher in patients with grade 3 and grade 4 dysphagia at baseline.

For non-responders, the changes at one month in dysphagia grade are outlined in the next table. Most had no data or no change:

Dysphagia Non-Responders, Analysis of one month data

Change in Dysphagia Grade (1 month)	PDT	YAG
Nothing Recorded	44	46
No Change	27	29
+1 grade	5	7
+2 grade	1	1
+3 grade	1	

As shown, about 40% of the patients in each arm had no followup measurement of dysphagia grade at one month. The large number of patients with no followup up data makes any statistical analysis of comparison between the two arms meaningless.

The fact that so few patients who had data recorded actually progressed may be a sort of internal

validity-check on the 'Dysphagia Grade Instrument.' If the variance of the measurement was large, one would expect large numbers of patients with positive and negative changes. This finding of relatively few with measurements documenting worsening might suggest that patients who were worsening never returned for followup assessment. This would suggest that the method is measuring a phenomenon which is correlated with patient behavior as one would expect (worsening dysphagia correlating with failure to return for followup). As an example, on the PDT arm 40 patients were recorded as improving whereas only 7 were recorded as worsening.

The properties of the dysphagia scale are not clear. For instance is the scale linear; ie is a change from grade 2 to grade 3 of equal value (clinical significance) to a change from 3 to 4? To help display and clarify the clinical meaning of the data the following table was prepared. It allows the viewer to make a subjective decision about the relative clinical worth of each change that could occur in dysphagia grade, and displays the number of patients in each arm experiencing such changes. In this way a viewer may tabulate the number of patients with clinically significant change in dysphagia grade according to the viewers own clinical experience.

The following table summarizes the data on responders by arm and according to individual starting-grade and ending-grade. To the left of the table are text that explain the clinical meaning.

Dysphagia Responses; Clinical meaning of 1-month data

Grades of Dysphagia; Defining symptoms	# of PDT Responders:	9*	6	4	9	5	6	1	40
	# of YAG Responders:	9	4	3	6	10	3	0	35
Patient can swallow:	**Dysphagia Grade**								
All *solids.**	1*	X*		X			X	X	
Some *solids.**	2*	↑*	X	↑		X	↑	↑	
No *solids; liquids* without difficulty.	3		↑	↑	X	↑	↑	↑	
Liquids with difficulty.	4				↑	↑	↑	↑	
No *liquids.*	5							↑	

*Example discussed in text.

To read this table, select the change of interest (for instance grade 2 changing to grade 3 starting at the arrow and ending up at the top X). The clinical meaning of this change can be found in the left column (for this example dysphagia grade changes at one month to CAN SWALLOW some SOLIDS to CAN SWALLOW SOLIDS). At the top of the table one finds the number of responders in each arm with this finding at one month (in this example 9 PDT patients and 9 YAG patients had such responses).

The duration of response as derived from the primary electronic data is described in the following table.

Study arm	# of Responders at 1 month	# responders with any followup value	# with continued response >= 2mo.
PDT	40	19	10
YAG	35	15	10

Only 1/3 to 1/2 of the patients in either arm with response at 1 month had any followup dysphagia grade recorded at 2 months or greater. Only 10/40 responders (or 10/118 patients) had response documented for 2 months or more on the PDT arm (6 for 2 months, 2 for 3 months and 2 for 6 months).

6.1.4.2 Objective Response

Objective response based on Lumenal diameter:

Methodology for response is discussed by the sponsor in volume 1.33 p 65, results on p 156, statistical methods in vol. 1.34 p 286, and tabulations in vol. 1.35 p 153.

Sponsor's method of analysis:

For practical reasons, the protocol-specified definition of response, which included length of tumor, bidimensional measurements of tumor, and change in lumenal diameter, was dropped. Investigator response was listed but not analyzed. Only luminal diameter was used unless CR1 (biopsy negative CR) was noted in which case this was also scored a response. In determining response, comparisons were made to best response after treatment. If lumen was dilated at endoscopy, pre-dilation lumen diameter was used.

The sponsor's intent to treat analysis is displayed in the following table 12 K from the submission:

Table12K.
Distribution of Objective Response at Week 1 and Month 1 During the First Course by Treatment Group

	All Available Assessments			
VISIT/ GRADE	PDT NO. PTS.	(%)	Nd:YAG NO. PTS.	(%)
Baseline	118	100	118	100
Week 1	118	100	118	100
CR1	2	1.7	1	0.9
CR2	0	0.0	0	0.0
PR	51	43.2	46	39.0
SD	28	23.7	26	22.0
PD	4	3.4	1	0.9
Missing	33	28.0	44	37.3
CR+PR (rate)[1]		44.9		39.8
(95% C.I.)				
Within Grp.[2]		(35.8, 53.3)		(30.9, 49.3)
Between Grp.[3]		5.09 (-7.61, 17.79)		
Month 1	118	100	118	100
CR1	1	0.9	0	0.00
CR2	1	0.9	0	0.00
CR3	0	0.00	0	0.00
PR	36	30.5	24	20.3
SD	18	15.3	17	14.4
PD	13	11.0	16	13.6
Missing	49	41.5	61	51.7
CR+PR (rate)[1]		32.2		20.3
(95% C.I.)				
Within Grp.[2]		(23.90, 41.43)		(13.49, 28.73)
Between Grp.[3]		11.86 (0.63, 23.09)		

1. Denominator for response rate=number of randomized patients
2. 95% confidence interval for treatment group response rate
3. 95% confidence interval for difference between response rates of the treatment groups (PDT-Nd:YAG). The O'Brien-Fleming method was used to adjust the width of the confidence interval.

According to the sponsor's analysis the response rate at 1 week was 45% for PDT and 40% for YAG. At 1 month this had decreased to 32% and 20% respectively. Differences between arms were not statistically significant at 1 week; at 1 month, unadjusted analysis is significant since

95% ci of difference in response rate on the 2 arms does not span zero.

Reviewer Comments:

The quality of followup data, with 30 to 50% of data points missing, is inadequate to allow statistical comparison. Within group findings, such as the finding of a minimal estimate of response, are still valid.

The sponsor considered only 72 or 73 patients evaluable in each arm. The analysis using evaluable patients gave rates that were 20% higher than the intent to treat analyses. On pp 160 to 172 of Volume 1.33 the sponsor does an examination of response by arm for subgroups according to tumor location, tumor size, previous therapy, investigator site. These analyses were unrevealing.

Reviewer analysis of Data Quality:

The sponsor's analysis of objective response was determined by the sponsor using minimal luminal diameter. The number of patients with such a measurement at different times as extracted from the data base is as follows:

Measurement	PDT: No. of pts	YAG: No. of patients
BASELINE	78	110
TREATMENT	34	9
WEEK0001	87	73
MONTH001	71	62
MONTH002	24	20
MONTH003	12	8
MONTH006	2	5

As shown, there is an imbalance in the number of patients with baseline measurements and 'treatment' measurements. Both of these were used as baseline measurements in the sponsor's analysis of response. Only 78/118 (66%) of the PDT arm patients had the baseline measurement recorded. Only 60% of patients had measurements at one month and less than 20% had a measurement at 2 months.

My preferred analysis, comparing measurements done at 1 month to those done at baseline, differed from the sponsor's analysis:

Number of Responders (lumen) at 1 month

	PDT	YAG
QLT analysis	38	24
M.O. analysis	36	24

Although the total counts were similar, there were disagreements in the classification of response on the following individuals:

243	264	2047	253
251	673		1921
650	827	826	1968
660	1762	903	2042
2504	1983	1703	2501

The sponsor classified some responders as such on the basis of using a 'Treatment' measurement as a baseline measurement.

The sponsor classified response based on the previous measurement instead of being compared to baseline. Examples of where this classification led to spurious response classifications:

Patient	Baseline	1 Week	1 Month	Sponsor Classification
243	0.6	1.0	0.6	Although there was no change from baseline at one month, this was classified as response at one week with stable disease at one month yielding an overall 1 month response classification.
660	0.2	1.3	0.6	Although the change from baseline at one month was 300%, the change from week 1 led to classification of progressive disease at one month..

Conclusions regarding data on luminal diameter:

Again one must conclude that the quality of the data is not sufficient to permit statistical

comparison of the 2 arms. Perhaps there is a suggestion that PDT produces a higher one month response rate (defined as 50% increase in lumenal diameter), but one can certainly not pretend to know definitively or with precision. In addition, the clinical significance of this endpoint is not clear. The clinical significance of the 1 week response data is even less clear. Data is insufficient to allow comment on duration of response..

One must also acknowledge that lumenal measurement was originally intended to be one part of an aggregate endpoint, and that data on the other portion (tumor measurements) was of even of poorer quality. The degree of reproducability of lumenal measurements was not addressed in the application.

However, despite all the caveats, about 1/3 of the patients randomized to PDT obtained a documented response as defined by a 50% increase in luminal diameter at one month. If such a finding were felt to be indicative of, or a surrogate for, clinical efficacy, then the findings could be supportive as evidence of efficacy.

6.1.4.4 Reviewer analysis of Dysphagia Response compared to Lumenal response:

The first analysis on the following page compares numbers of responders by the 2 previous methods of assessment, change in lumenal diameter or change in dysphagia grade. In this analysis, all patients were included. Patients with data missing at baseline or at one month were listed as non-responders for that method. There were 236 patients in this analysis, 118 on each arm. Superficial examination suggests that the 2 methods show a strong correlation, especially in identifying non-responders (136 patients identified by both methods as non-responders).

However, this analysis is biased. Since both measurement methods required followup data for scoring a response; lack of followup data was scored by a non-response by both methods. For this reason, the second analysis on the following page includes data from patients who were 'evaluable' by both methods, ie patients with complete data for baseline and one month followup by both methods. There were 110 such patients. The 2 analyses are compared in the following presentation:

Cross validation of 2 methods of response* assessment:

Lumenal diameter versus Dysphagia grade

Population: All patients

	Luminal responder	Luminal non-responder	Total
Dysphagia responder	35	40	75
Dysphagia non-responder	25	136	161
Total	60	176	236

Population: Patients with complete data for *both* methods**

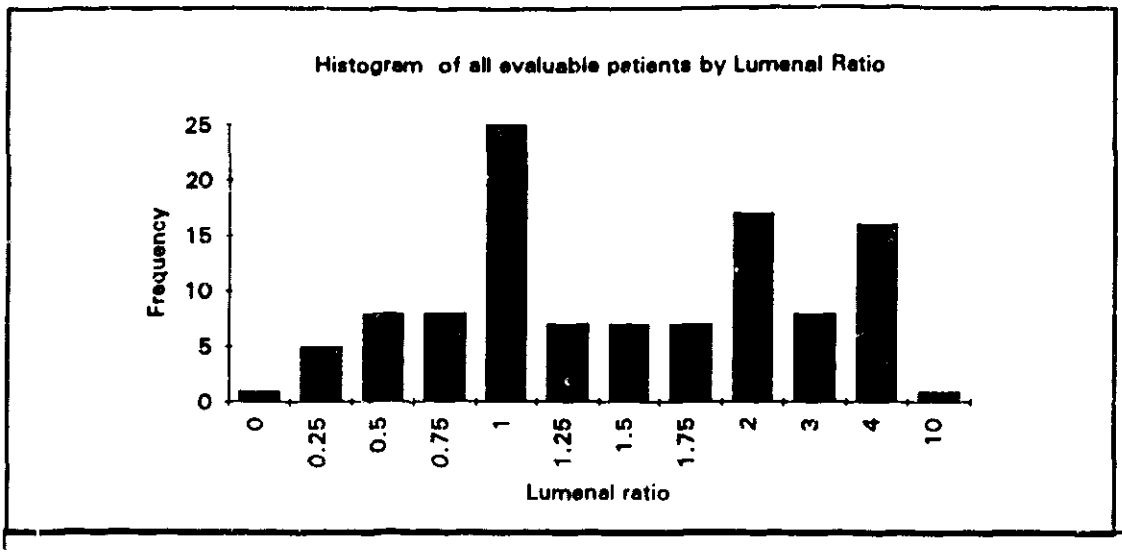
	Luminal responders	Luminal non-responders	Total
Dysphagia responders	35	21	56
Dysphagia non-responders	24	30	54
Total	59	51	110

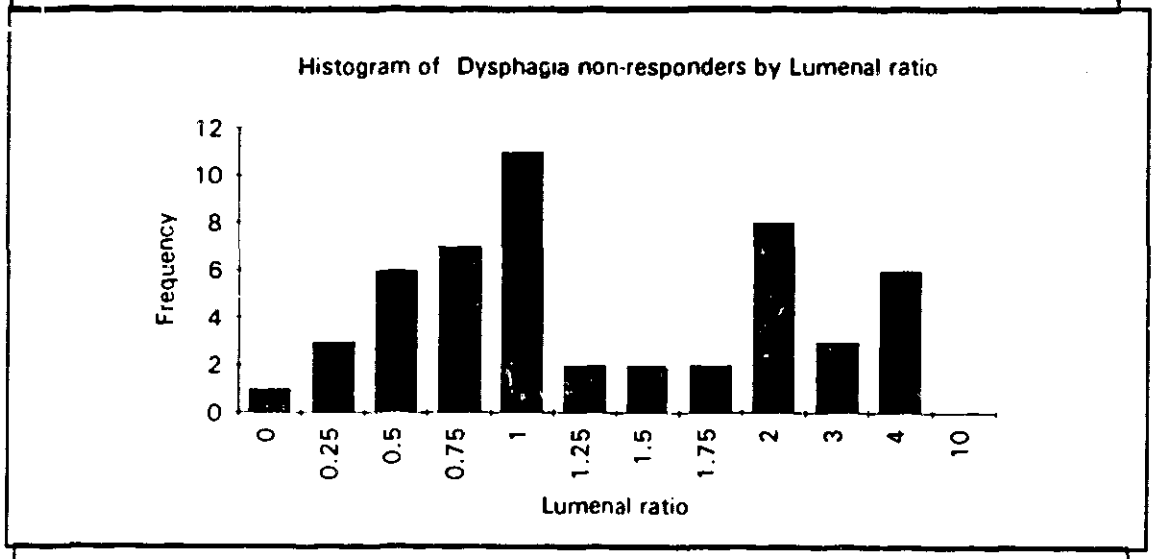
*Response at one month.
**Complete data was defined as having an entry for 'baseline' and 'month001' for both methods.

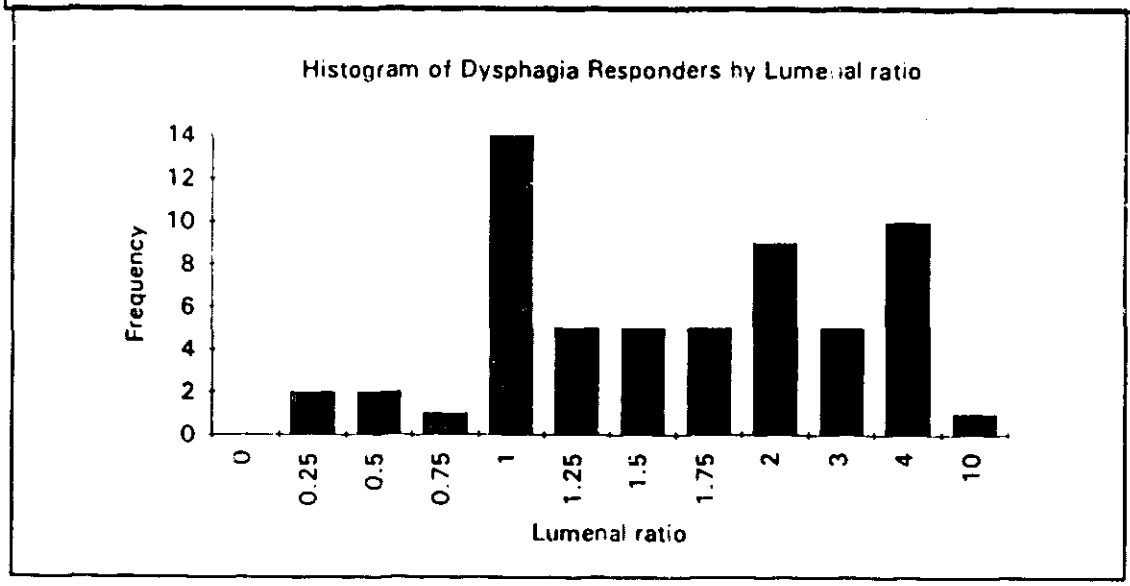
The 2X2 table of the 110 'evaluable' patients shows less asymmetry. In this group of patients, the trend for one method of measuring response to predict response as determined by the other method is only a trend (($p = 0.06$ by chi-square).

A histogram of number of patients grouped by 'Lumenal ratio' (diameter at one month/diameter at baseline) in this population of 110 'evaluable' patients at one month is presented in the following 3 graphs. Respectively, the 3 histograms are from the entire evaluable population, the dysphagia responders alone, and the dysphagia non-responders alone.

The histogram distributions are remarkably similar overall, however frequency of patients with a lumenal ratio less than one appears to be greater in non-responders than in responders.


Histogram of all evaluable patients by Lumenal Ratio
Frequency
25
20
15
10
5
0
0
0.25
0.5
0.75
1
1.25
1.5
1.75
2
3
4
10
Lumenal ratio


Histogram of Dysphagia non-responders by Lumenal ratio
Frequency
12
10
8
6
4
2
0
0
0.25
0.5
0.75
1
1.25
1.5
1.75
2
3
4
10
Lumenal ratio

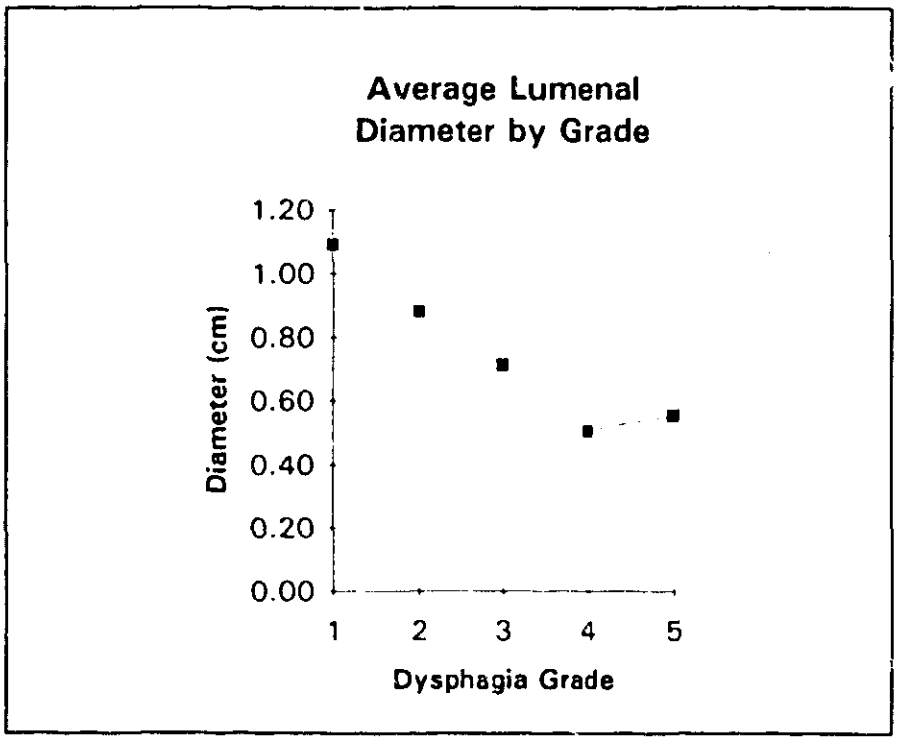

Histogram of Dysphagia Responders by Lumenal ratio
Frequency
14
12
10
8
6
4
2
0
0
0.25
0.5
0.75
1
1.25
1.5
1.75
2
3
4
10
Lumenal ratio

Lumenal diameter compared to Dysphagia Grade

The previous analyses have concentrated on response categorized by pre-specified criteria. An important concept in analyzing subjective data such as dysphagia grade, especially when observers are not blinded to treatment, is whether there are physical findings to corroborate the subjective data; i.e. subjective data is associated with the disease state rather than possibly just representing observer bias. The following analyses examine the relationship between dysphagia grade and lumenal diameter, and between change in dysphagia grade and change in lumenal diameter. Such analyses, not limited to patients evaluable for response, allow inclusion of more data elements than previous analyses.

All patient visits in the data set which had both dysphagia data and lumenal diameter data were used in the following analysis.

Dysphagia Grade	Number of Observations	Lumen Diameter (avg)	St dev
1	112	1.09	0.41
2	245	0.88	0.42
3	93	0.71	0.36
4	91	0.51	0.36
5	14	0.55	0.44



There is obviously an inverse correlation between lumenal diameter and dysphagia grade, at least for grades 1-4. However, there is large variation in individual data as indicated by standard deviations.

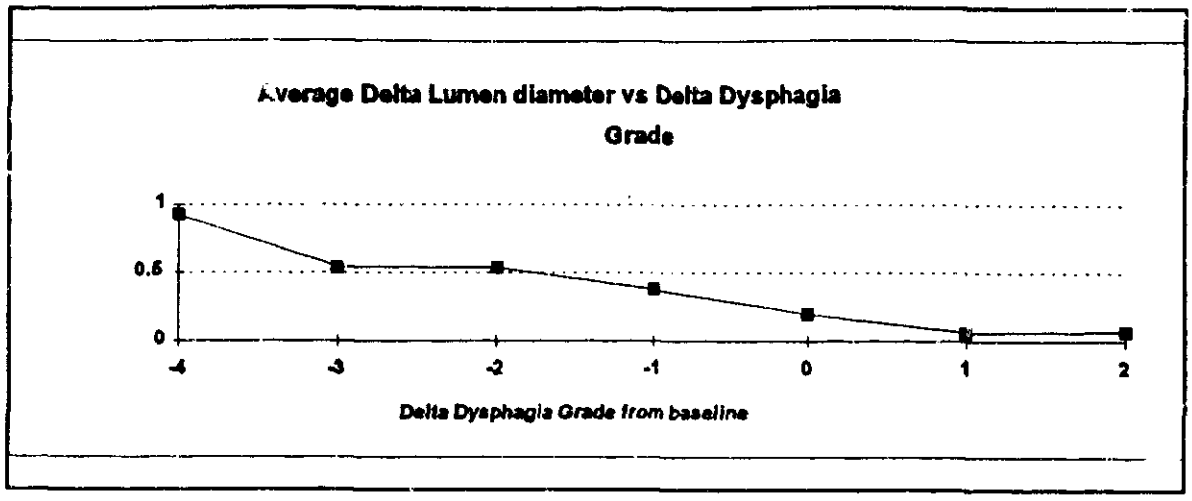
Correlation between change in dysphagia grade and change in lumenal diameter:

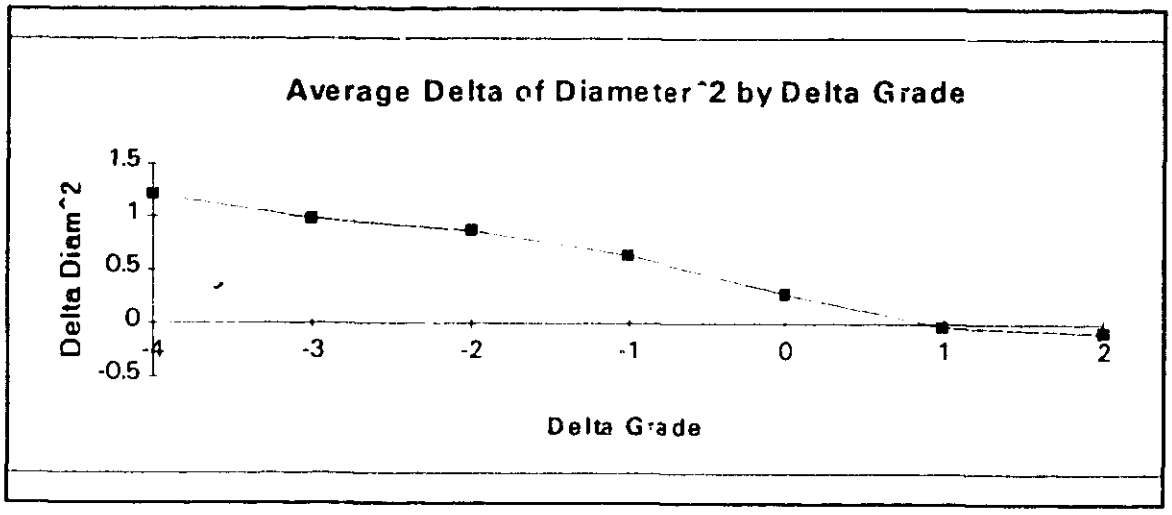
Above analyses support the fact that the subjective measurement of dysphagia grade is related to physical measurement of lumenal diameter in a population. However, response as described in this protocol is not based on absolute dysphagia grade, but on change from baseline in dysphagia grade. Therefore, another pertinent question in validating the dysphagia scale is what is the relationship in individual patients between 'dysphagia grade change from baseline' and' lumenal diameter change from baseline.'

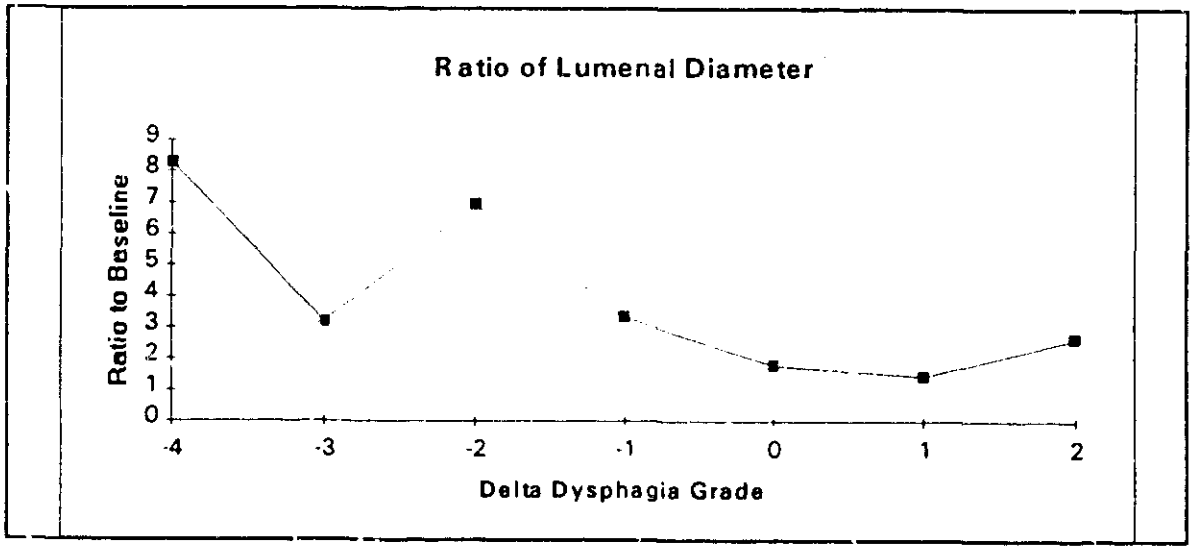
The following analyses used all baseline records with followup data from all followup times (1 week, 1,2,3 and 6 months). Thus 308 followup data points were available to calculate 'delta dysphagia grade' and 'delta lumenal diameter.' Also analyzed were delta[(luminal diameter)^2] and ratio of luminal diameter to baseline luminal diameter. The latter was the basis for the protocol defined luminal response (i.e ratio to baseline of 1.5 or greater).

Delta Dysphagia Grade	No. of data points	Avg. of Delta Lum.Diam.	sdev	Avg of Delta of (Lum Diam)^2	sdev	Avg Ratio of Lum Diam.	sdev
-4	2	0.92	0.39	1.21	0.7	8.3	6.65
-3	20	0.54	0.56	0.98	1	3.2	2.38
-2	49	0.54	0.41	0.86	0.8	6.96	21.17
-1	91	0.38	0.41	0.64	0.8	3.35	10.39
0	120	0.2	0.49	0.28	1.1	1.8	1.5
1	19	0.06	0.46	0	0.9	1.45	0.93
2	7	0.07	0.81	-0.1	1.5	2.65	2.45

The graphical dysplays of delta dysphagia grade and these three measures of change in lumenal diameter are presented on the next page.


Average Delta Lumen diameter vs Delta Dysphagia Grade
1
0.5
0
-4
-3
-2
-1
0
1
2
Delta Dysphagia Grade from baseline


Average Delta of Diameter^2 by Delta Grade
Delta Diam^2
1.5
1
0.5
0
-0.5
-4
-3
-2
-1
0
1
2
Delta Grade


Ratio of Lumenal Diameter
Ratio to Baseline
9
8
7
6
5
4
3
2
1
0
-4
-3
-2
-1
0
1
2
Delta Dysphagia Grade

Visual inspection would suggest that change from baseline in dysphagia grade is inversely related to change in lumenal diameter by these three methods when data are averaged according change in dysphagia grade. The association appears most uniform for delta[(luminal diameter)^2].

Conclusions from Reviewer Analyses of Efficacy Data

Quality (completeness) of efficacy data is clearly not sufficient to support statistical analyses comparing the 2 arms. Comparison of the individual patient's dysphagia grades at one month with the patient's corresponding value at baseline suggests that one third to one half of patients in both groups, especially those with higher grades of baseline dysphagia, had a decrease in dysphagia grade at one month. Data is insufficient to allow comment on duration of response. Examination of the relationship between dysphagia grade (as reported by patient/physician) to lumenal diameter (as measured by endoscopist) suggests that the dysphagia grade does, on average, correlate with lumenal diameter. Similarly, on average, change in dysphagia grade correlates with change in lumenal diameter. However, variation in the data on an individual basis is large.

In my opinion, the answer to the question:

'Has efficacy been shown?'

depends on one's subjective assessment of the importance of the data underlined in the following table (reproduced from earlier in the review). The number of responding Pdt patients in each category (40 in all) is underlined. There were originally 118 patients in each arm.

Dysphagia Responses; Clinical meaning of 1-month data

Grades of Dysphagia; Defining symptoms	# of Pdt Responders:	9	6	4	9	5	6	1	40
	# of YAG Responders:	9	4	3	6	10	3	0	35
Patient can swallow:	Dysphagia Grade								
All *solids*.	1	X		X			X	X	
Some *solids*.	2	↑	X	↑		X	↑	↑	
No *solids; liquids* without difficulty.	3		↑	↑	X	↑	↑	↑	
Liquids with difficulty.	4				↑	↑	↑	↑	
No *liquids*.	5							↑	

Survival

85% of the patients on each arm were dead at the time of analysis, with about 10% of the patients lost to followup on each arm. Median survival was about 4 months on each arm. Survival curves were nearly identical (Hazard ratio = 1.0, 95% ci 0.74-1.28). The data are summarized in the sponsor's table 12Y:

Table 12Y. Summary of Survival for All Patients by Treatment Group

	PDT		Nd:YAG	
	NO. PTS.	(%)	NO. PTS.	(%)
Randomized	118	100.0	118	100.0
Number Dead	103	87.3	101	85.6
Number Censored	15	12.7	17	14.4
Alive	4		8	
Lost to follow-up	11		9	
Median TTF (days) [95% C.I.][a]	123	[94,148]	140	[112,176]
Range				
Wilcoxon Chi-square (1 df)/p-value	0.190/0.6626			
Mantel-Cox Chi-square (1 df)/p-value	0.042/0.8371			
Hazard Ratic (Nd:YAG/PDT)[c]	0.97			
[95% CI]	[0.74,1.28]			

[a] Brookmyer - Crowley Method.
[b] Censored observation.
[c] Adjusted for using O'Brian-Fleming procedure.

6.1.5 Safety Analysis:
6.1.5.1 Deaths

Treatment related deaths are tabulated by cause of death in the Sponsor's table 13A:

Table 13A. Number (Percentage) of Randomized Patients Who Died, by Cause of Death and Treatment Group

	PDT			Nd:YAG		
	All		Tx-Related*	All		Tx-Related*
	No	(%)	No.	No.	(%)	No.
No. Randomized	118	(100)		118	(100)	
No. Dead	103	(87)	6	101	(86)	0
Cause of Death						
Progressive Disease	61	(52)	1**	72	(61)	0
Unknown	11	(9)	0	8	(7)	0
Infection	5	(4)	2	5	(4)	0
Congestive Heart Failure	3	(3)	1	1	(1)	0
Esophageal/GI Hemorrhage	3	(3)	1	0	(0)	0
Myocardial Infarction	3	(3)	0	2*	(2)	0
Stroke/Brainstem Infarct	3	(3)	0	1	(1)	0
Aspiration Pneumonia	3	(3)	0	1	(1)	0
Cardiac Arrest	2	(2)	0	1	(1)	0
Other	1	(1)	0	1	(1)	0
Hematemesis	1	(1)	0	2	(2)	0
Lung Carcer	1	(1)	0	0	(0)	0
Metastatic PD	1	(1)	0	1	(1)	0
Pneumonia	1	(1)	0	3	(3)	0
Respiratory Failure	1	(1)	0	0	(0)	0
Tracheoesophageal Fistula	1	(1)	1	0	(0)	0
Hypercalcemia	1	(1)	0	1	(1)	0
Massive Pulm. Bleed	1	(1)	0	1	(1)	0
Cholecystitis	0	(0)	0	1	(1)	0

* Treatment-relationship assigned by the Investigator; includes events classified as definitely, probably and possibly related to treatment.

** Patient No. experienced numerous adverse events prior to death which the Investigator judged as probably or possibly related to treatment.

* Patient No. 241/8 had myocardial infarction and pneumonia listed as cause of death.

Deaths due to progressive disease were slightly more frequent on YAG arm(72 pts vs 62). Deaths grouped together (by reviewer) due to ischemic causes (MI, Stroke, Cardiac arrest) were more common on the Pdt arm (8 versus 4 deaths), but this difference was not statistically significant. 6 deaths were possibly treatment associated as judged by the investigator on the PDT arm compared to none on the YAG arm (p = 0.04 by chi square). These are listed below:

Pdt Pts. with deaths considered at least 'Possibly' Treatment-related:

Pt. #	Cause of Death	Treatment Relationship	Course	Days from last Rx.	Survival (days)
	CHF	Possible	2	1	40
	Infection	Possible	2	2	129
	Prog Dz	Possible	1	27	32
	GI bleed	Possible	1	27	32
	Infection	Definite	1	30	39
	Tracheo-esoph. fist.	Probable	1	79	87

Further information on these deaths was located in several places in the NDA:

Vol 35	Appendix V	Clinical capsules of pt. deaths.
36-37		Patient Profile
107-115		Case report forms.

Review of Deaths on PDT arm:

•

On second course of PDT, this pt. developed pulmonary infiltrates starting 1 day after the photofrin injection, progressing to cardiopulmonary deterioration over next 2 days. I consider this possibly related to photofrin injection. This is listed as CHF, but it seems likely to me that it was

ARDS. Note that the first signs of this systemic reaction occurred prior to laser.

This patient died 26 days into the second course of PDT. Autopsy showed an esophagopleural fistula. Death was probably from associated infection.

This patient developed pneumonia from TE fistula occurring the first week of therapy. Bleeding from necrotic tumor was not treated at request of family as the terminal event, however I consider the TE fistula and infection as major factors.

This patient with a tumor at 20 cm died on day 32 unexpectedly of massive upper GI bleed. No autopsy was done.

This patient had TE fistula at one week and died with pseudomonas pneumonia on day 39.

This patient died on day 87 from complications of a TE fistula first noted about day 30.

Removal From Study for adverse experiences:

10 to 15% of the patients on each arm were removed for adverse experiences as shown in the sponsor's table 13D:

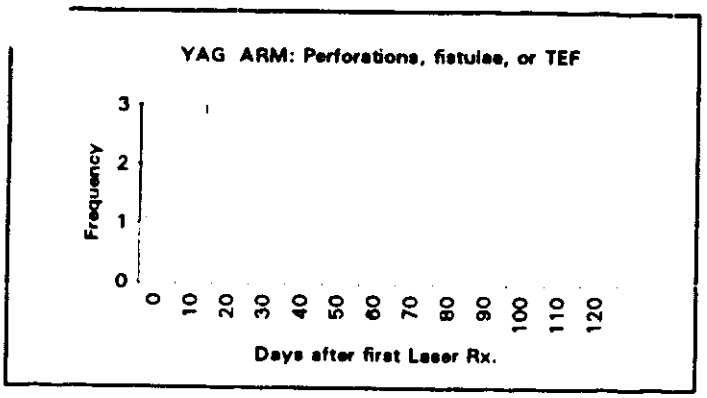
Table 13D. Number (Percentage) of Treated Patients Who Were Removed From Study Due to an Adverse Event, By Type of Event and Treatment Group

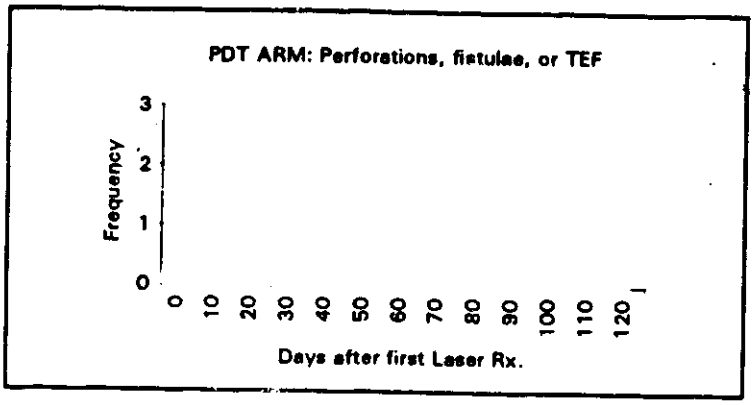
	PDT All No.	PDT All (%)	PDT Tx-Related* No.	YAG All No.	YAG All (%)	YAG Tx-Related* No.
No. Treated		(100)		108	(100)	
Total No. Removed for Adverse Event	(12)		6	17	(16)	7
Adverse Event						
Fistula	(8)		5	8	(7)	4
Anemia	(1)		0	0	(0)	0
Fracture	(1)**		0	0	(0)	0
Laryngotracheal Edema	(1)		1	0	(0)	0
Suspected Perforation	(1)		0	0	(0)	0
Esophageal Perforation	(0)		0	3	(3)	3
Pleural Effusion	(0)		0	1	(1)	0
Worsening COPD	(0)		0	1	(1)***	0
Stroke	(0)		0	2	(2)	0
Atrial Flutter	(0)		0	1	(1)	0
Esophageal Stricture	(0)		0	1	(1)+	0

COPD = Chronic Obstructive Pulmonary Disease
* Treatment-relationship assigned by the investigator; includes events classified as definitely, probably and possibly related to treatment.
** Off-study reason in the case report form was listed as "other: concurrent illness".
*** Off-study reason in the case report form was listed as "other: patient deterioration".
\+ Off-study reason in the case report form was listed as "other: adverse experience".

The occurrence of fistulae was the most common problem, occurring in 7-8% of the patients in each arm.

One pt. on the PDT arm was removed from study for Laryngo-tracheal edema (1922/22). 3 on the Yag arm were removed for esophageal perforation. The individual patients removed from study for adverse reactions are listed in attached tables 13E and 13E from the Sponsor's Study report. If the different problems involving the wall of the esophagus are combined (Fistula, TEF, and perforation), there are 10 such events on the PDT arm and 11 on the YAG arm. The following histograms suggest that the timing of the events are similar, perhaps with a trend toward earlier events occurring on the YAG arm.





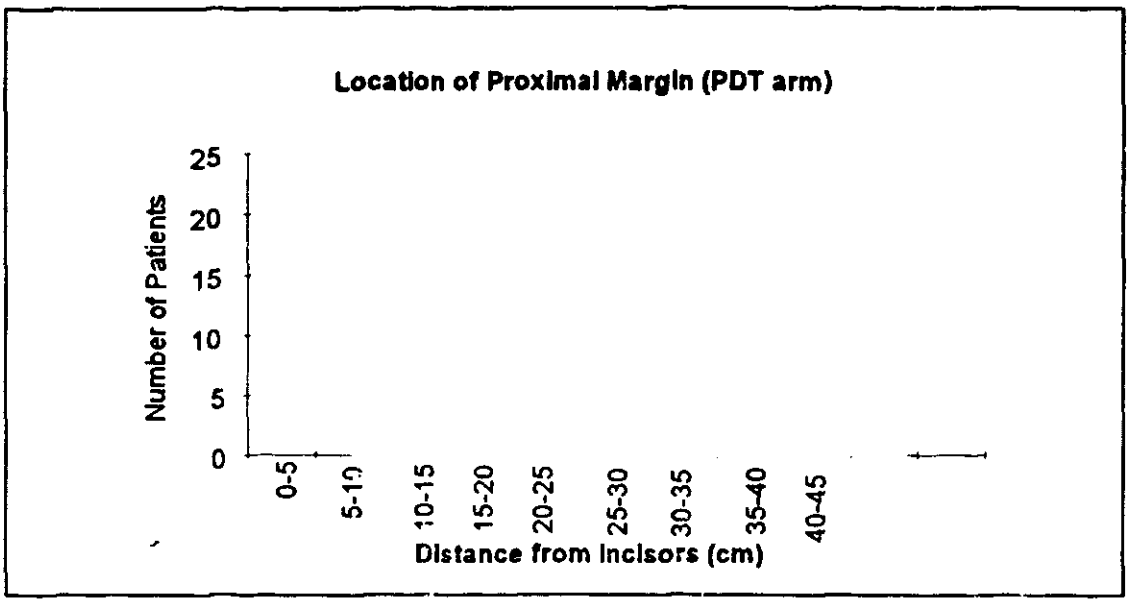
Narratives and tabulations on the individuals
on the PDT arm were reviewed. Notes on these patients can be found in the appendix of this review. One patient was of special interest:

Patient

This patient had laryngo-tracheal edema on day 3 of course 1, three and one half hours after laser therapy. Her tumor was located from 14-18 cm from the incisors. Laryngeal edema required emergency tracheostomy ; this was subsequently closed after 30 days. Although dysphagia decreased and this patient was classified as a partial response, it is unlikely that the patient received net benefit from PDT therapy.

Reviewer comments:

It seems logical that this reaction is related to the proximity of the tumor to the laryngeal area. Indeed, when patients were sorted according to distance of proximal margin of tumor from incisors, this patient had the most proximal tumor of the 83 patients on the PDT arm who had such measurements recorded at baseline.(SAS data set, table VIIF).The distribution of number of patients according to distance of tumor from incisors is shown in the following histogram:



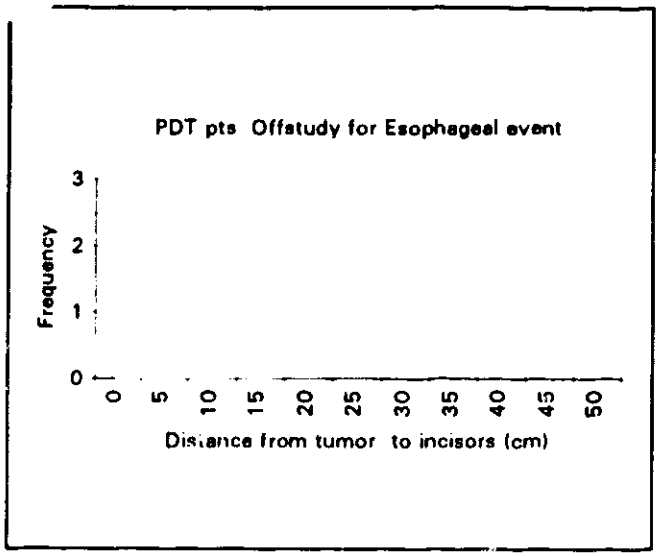
The adverse reaction data base was examined further for symptoms that might indicate upper airway obstruction. The following table lists the 4 patients with some reference to upper airway obstruction or symptoms. All were on the PDT arm, all had tumors from 14-20 cm from the incisors and all had the symptoms begin on days 3-5 (Laser energy is applied on day 3 of PDT therapy).

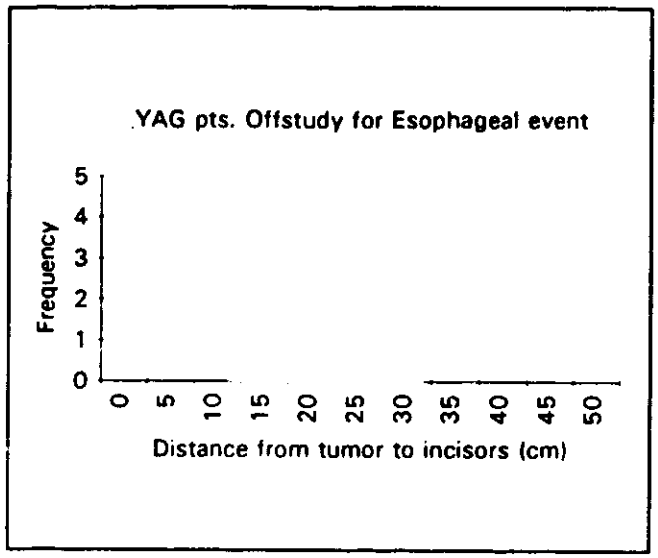
PT	CATEGORY	ADVERSE EVENT	AE TEXT	STUDY DAY	COURSE DAY	PROX MARG(CM)
	RESPIRATORY	STRIDOR	STRIDOR	3	3	18
	RESPIRATORY	RESPIRATORY INSUFFICIENCY	AIRWAY OBSTRUCTION	3	3	14
	RESPIRATORY	DYSPNOEA	STRIDOUROUS RESPIRATIONS	45	3	18
	RESPIRATORY	LARYNGEAL SWELLING	LARYNX OEDEMA	5	5	20

These data suggest that special care should be used in following the airway of patients with proximal tumors treated with PDT.

There were 22 patients in the data base who had 'esophageal' events causing them to go offstudy. The distribution of these patients in the 2 arms is shown in the following histograms. The similarity to the histogram of the full population suggests that location is not a primary

determinant of frequency of esophageal event in either arm.





6.1.5.2 Incidence of Adverse Experiences:

Data conventions are described in the 6-14-94 submission (part 5.0) and V. 1.34 (appendix III).

Adverse events were recorded as specific signs or symptoms on the CRFs. A WHO dictionary was used to classify them. Modifications for esophageal cancer are discussed in section 2.4.2 of the manual. Adverse laboratory events were not included unless symptoms were involved (anemia, hypokalemia, hypoglycemai, hypocalcemai, and hypercalcemai). Causality was recorded by the investigator (definitely, probably, possibly, remotely related to study treatment).

The WHO dictionary was altered with regard to esophageal events:

- odynophagia was coded as pharyngitis if no dysphagia was present;
- -Esophageal perforations were coded as esophageal ulceration.
- -Esophageal pain was coded as chest pain.

Clinical Adverse Experiences

The sponsor lists the incidence of adverse experiences classified by system and AE in table 13.3.1.1 of the NDA. The number of patients with at least one adverse event was similar on the 2 arms (92 % PDT and 82% YAG). Table 13 G from the submission (attached) summarizes the differences in incidence between arms of at least 5%. The following table extracts those differences significant at $p<0.01$ level (Wilcoxon test on numbers grouped by severity grade):

No. Pts. Rx	PDT	YAG
Total	110	108
Adverse Event		
Photosensitivity	21	0
Constipation	25	10
All myo-endo-pericardial and valve	6	0
All Respiratory	68	44
Pleural effusion	31	6
Respiratory Insufficiency	11	1
Anemia	29	13
Fever	36	11

Severe and life-threatening Adverse events:

Attached table 13H lists Severe and Life-threatening events. Although the incidence of number of both Severe and LT events was similar on the 2 arms (52% vs 45%), the incidence of life threatening events was significantly greater on PDT (29% vs 15%, p= 0.02).

No. Pts. Rx	PDT		YAG	
Total	110		108	
	Severe	LT*	Severe	LT
No. with severe or LT AE	25	32	33	16

*Life threatening

Table 13G. Number (Percentage) of Treated Patients Reporting at Least One Adverse Event, by Body System, Individual Adverse Experience (Preferred Terms) Within Body System, and Treatment Group: Events For Which the Treatment Difference in Incidence is at least 5%. Based on All Treated Patients

	PDT No. (%)	Nd:YAG No. (%)	Treatment Comparison p-value*
No. of Treated Pts.	(100)	108 (100)	
At Least One Adverse Experience	(91.8)	88 (81.5)	p =0.02
Type of Event			
All Skin and Appendages	(25.5)	8 (7.4)	p <0.01
Photosensitivity Reaction	(19.1)	0 (0.0)	p <0.01
All Autonomic Nervous System	(14.5)	9 (8.3)	p =0.15
All Gastrointestinal	(66.4)	56 (51.9)	p =0.05
Abdominal Pain	(19.1)	12 (11.1)	p =0.11
Constipation	(22.7)	10 (9.3)	p <0.01
Nausea	(20.9)	16 (14.8)	p =0.25
Esophageal Ulceration**	(0.9)	7 (6.5)	p =0.03
Vomiting	(15.5)	9 (8.3)	p =0.10
All Metabolic & Nutritional	(16.4)	10 (9.3)	p =0.14
Weight Decrease	(7.3)	2 (1.9)	p =0.06
All Myo-,Endo-,Pericardial & Valve	(5.5)	0 (0.0)	p =0.01
All Heart Rate/Rhythm	(16.4)	12 (11.1)	p =0.23
All Respiratory	(61.8)	44 (40.7)	p <0.01
Pleural Effusion	(28.2)	6 (5.6)	p <0.01
Respiratory Insufficiency	(10.0)	1 (0.9)	p <0.01
Pharyngitis	(9.1)	4 (3.7)	p =0.12
All Red Blood Cell	(26.4)	13 (12.0)	p <0.01
Anemia	(26.4)	13 (12.0)	p <0.01
All Urinary	(14.5)	9 (8.3)	p =0.15
All Body as a Whole	(68.2)	58 (53.7)	p =0.26
Fever	(32.7)	11 (10.2)	p <0.01
Oedema Generalized	(7.3)	2 (1.9)	p =0.06
All Resistance Mechanism	(15.5)	7 (6.5)	p =0.04

* Treatment groups were compared with respect to the distribution of ordered severity scores (none, mild, moderate, severe, very severe/life-threatening) using a (two-sided) Wilcoxon test.
** This adverse experience was reported for more Nd:YAG-treated patients than PDT-treated patients.

References: Appendices IV, X.D

Table 13H. Number (Percentage) of Treated Patients Reporting At Least One Severe or Life-Threatening Adverse Event, by Body System, Individual Adverse Experience Within Body System and Treatment Group

	PDT				Nd:YAG			
	Total		Severe	LT*	Total		Severe	LT*
	No.	(%)	No.	No.	No.	(%)	No.	No.
No. Treated	110	(100)			108	(100)		
At Least One Severe or Life-Threatening AE	57	(51.8)	25	32	49	(45.4)	33	16
Type of Event								
All Skin and Appendages	0	(0.0)	0	0	1	(0.9)	0	1
Cellulitis	0	(0.0)	0	0	1	(0.9)	0	1
All Musculo-Skeletal	2	(1.8)	2	0	1	(0.9)	1	0
Arthralgia	1	(0.9)	1	0	0	(0.0)	0	0
Bone Disorder	0	(0.0)	0	0	1	(0.9)	1	0
Fracture Pathological	1	(0.9)	1	0	0	(0.0)	0	0
All Central Nervous System	4	(3.6)	3	1	1	(0.9)	1	0
Convulsions	1	(0.9)	0	1	0	(0.0)	0	0
Hypokinesia	1	(0.9)	1	0	0	(0.0)	0	0
Headache	1	(0.9)	1	0	0	(0.0)	0	0
Optic Neuritis	1	(0.9)	1	0	0	(0.0)	0	0
Paralysis	0	(0.0)	0	0	1	(0.9)	1	0
All Autonomic Nervous System	6	(5.5)	4	2	1	(0.9)	1	0
Glaucoma	1	(0.9)	1	0	0	(0.0)	0	0
Hypertension	2	(1.8)	2	0	0	(0.0)	0	0
Hypotension	2	(1.8)	1	1	0	(0.0)	0	0
Ileus	0	(0.0)	0	0	1	(0.9)	1	0
Syncope	1	(0.9)	0	1	0	(0.0)	0	0
All Vision	2	(1.8)	2	0	0	(0.0)	0	0
Eye Pain	1	(0.9)	1	0	0	(0.0)	0	0
Vision Abnormal	2	(1.8)	2	0	0	(0.0)	0	0
All Psychiatric	3	(2.7)	3	0	5	(4.6)	5	0
Amnesia	0	(0.0)	0	0	1	(0.9)	1	0
Anorexia	1	(0.9)	1	0	3	(2.8)	3	0
Agitation	1	(0.9)	1	0	0	(0.0)	0	0
Confusion	2	(1.8)	2	0	0	(0.0)	0	0
Insomnia	0	(0.0)	0	0	1	(0.9)	1	0
All Gastrointestinal	23	(20.9)	13	10	17	(15.7)	11	6
Abdominal Pain	5	(4.5)	5	0	5	(4.6)	5	0
Constipation	2	(1.8)	1	1	1	(0.9)	1	0
Diarrhea	1	(0.9)	1	0	0	(0.0)	0	0
Esophageal Stricture	2	(1.8)	2	0	1	(0.9)	1	0
Esophagitis	1	(0.9)	1	0	0	(0.0)	0	0
Dyspepsia	1	(0.9)	1	0	0	(0.0)	0	0

* LT = Life-threatening

References: Appendix X.D

Table 13H Continued. Number (Percentage) of Treated Patients Reporting At Least One Severe or Life-Threatening Adverse Event, by Body System, Individual Adverse Experience Within Body System and Treatment Group

	PDT			Nd:YAG		
	Total No. (%)	Severe No.	LT* No.	Total No. (%)	Severe No.	LT* No.
Dysphagia	2 (1.8)	2	0	2 (1.9)	2	0
Eructation	0 (0.0)	0	0	1 (0.9)	1	0
GI Hemorrhage	3 (2.7)	0	3	1 (0.9)	0	1
Hematemesis	5 (4.5)	2	3	2 (1.9)	0	2
Melena	1 (0.9)	0	1	0 (0.0)	0	0
Hiccup	0 (0.0)	0	0	1 (0.9)	1	0
Intestinal Stenosis	1 (0.9)	1	0	0 (0.0)	0	0
Esophageal Ulceration	0 (0.0)	0	0	3 (2.8)	0	3
Esophageal Ulceration Hemorrhage	2 (1.8)	1	1	1 (0.9)	1	0
Peritonitis	1 (0.9)	0	1	0 (0.0)	0	0
Stomatitis Ulcerative	1 (0.9)	1	0	0 (0.0)	0	0
Vomiting	4 (3.6)	4	0	2 (1.9)	2	0
All Liver and Biliary	4 (3.6)	3	1	1 (0.9)	1	0
Cholecystitis	2 (1.8)	1	1	1 (0.9)	1	0
Jaundice	2 (1.8)	2	0	0 (0.0)	0	0
All Metabolic and Nutritional	1 (0.9)	0	1	3 (2.8)	0	3
Acidosis	0 (0.0)	0	0	1 (0.9)	0	1
Dehydration	1 (0.9)	1	0	1 (0.9)	1	0
Hypercalcemia	1 (0.9)	0	1	1 (0.9)	0	1
Weight Decrease	0 (0.0)	0	0	1 (0.9)	0	1
All Cardiovascular	2 (1.8)	1	1	2 (1.9)	2	0
Cardiac Failure	2 (1.8)	1	1	2 (1.9)	2	0
All Myo-,Endo-, Pericardial and Valve	4 (3.6)	2	2	0 (0.0)	0	0
Endocarditis	1 (0.9)	1	0	0 (0.0)	0	0
Myocardial Infarction	2 (1.8)	0	2	0 (0.0)	0	0
Angina Pectoris	1 (0.9)	1	0	0 (0.0)	0	0
All Heart Rate/Rhythm	5 (4.5)	2	3	1 (0.9)	0	1
Cardiac Arrest	1 (0.9)	0	1	1 (0.9)	0	1
Fibrillation Atrial	4 (3.6)	2	2	0 (0.0)	0	0
Tachycardia	2 (1.8)	2	0	0 (0.0)	0	0
All Vascular (Extracardiac)	2 (1.8)	1	1	5 (4.6)	5	0
Cerebrovascular Disorder	1 (0.9)	0	1	5 (4.6)	5	0
Peripheral Ischemia	0 (0.0)	0	0	1 (0.9)	1	0
Thrombophlebitis	1 (0.9)	1	0	0 (0.0)	0	0
All Respiratory	30 (27.3)	12	18	18 (16.7)	12	6
Apnea	1 (0.9)	1	0	0 (0.0)	0	0
Aspiration	0 (0.0)	0	0	1 (0.9)	1	0
Chest X-ray Abnormal	1 (0.9)	1	0	0 (0.0)	0	0
Coughing	1 (0.9)	1	0	0 (0.0)	0	0

* LT = Life-threatening

References: Appendix X.0

Table 13H Continued. Number (Percentage) of Treated Patients Reporting At Least One Severe or Life-Threatening Adverse Event, by Body System, Individual Adverse Experience Within Body System and Treatment Group

	PDT				Nd:YAG			
	Total		Severe	LT*	Total		Severe	LT*
	No.	(%)	No.	No.	No.	(%)	No.	No.
Dyspnea	2	(1.8)	2	0	4	(3.7)	4	0
Pleural Effusion	3	(2.7)	3	0	3	(2.8)	3	0
Pneumonia	9	(8.2)	3	6	5	(4.6)	3	2
Pulmonary Infiltration	1	(0.9)	1	0	0	(0.0)	0	0
Pulmonary Edema	1	(0.9)	1	0	0	(0.0)	0	0
Respiratory Insufficiency	11	(10.0)	0	11	1	(0.9)	0	1
Hemoptysis	1	(0.9)	1	0	0	(0.0)	0	0
Pulmonary Hemorrhage	1	(0.9)	0		0	(0.0)	0	0
Stridor	1	(0.9)	1	0	0	(0.0)	0	0
Pharyngitis 4	1	(0.9)	1	0	1	(0.9)	1	0
Tracheoesophageal Fistula	9	(8.2)	3	6	7	(6.5)	2	5
All Red Blood Cell	6	(5.5)	5	1	4	(3.7)	4	0
Anemia	6	(5.5)	5	1	4	(3.7)	4	0
All Urinary	4	(3.6)	4	0	2	(1.9)	1	1
Hydronephrosis	0	(0.0)	0	0	1	(0.9)	1	0
Renal Failure Acute	0	(0.0)	0	0	1	(0.9)	0	1
Renal Function Abnormal	2	(1.8)	2	0	0	(0.0)	0	0
Urinary Tract Infection	2	(1.8)	2	0	0	(0.0)	0	0
All Body as a Whole	10	(9.1)	10	0	17	(15.7)	15	2
Ascites	1	(0.9)	1	0	1	(0.9)	1	0
Asthenia	0	(0.0)	0	0	3	(2.8)	3	0
Back Pain	1	(0.9)	1	0	0	(0.0)	0	0
Chest Pain	3	(2.7)	3	0	2	(1.9)	2	0
Chest Pain Substernal	1	(0.9)	1	0	1	(0.9)	1	0
Fatigue	0	(0.0)	0	0	1	(0.9)	1	0
Fever	3	(2.7)	3	0	1	(0.9)	0	1
Edema	1	(0.9)	1	0	0	(0.0)	0	0
Edema Generalized	1	(0.9)	1	0	2	(1.9)	1	1
Pain	2	(1.8)	2	0	6	(5.6)	6	0
All Resistance Mechanism	3	(2.7)	1	2	2	(1.9)	2	0
Infection	0	(0.0)	0	0	1	(0.9)	1	0
Sepsis	3	(2.7)	1	2	2	(1.9)	2	0

* LT = Life-threatening

References: Appendix X.0

The excess in LT events is primarily contributed by the GI (10 events versus 6 events) and Respiratory (18 events versus 6 events) systems. In the GI system, events including bleeding were a source of the difference between arms (7 events versus 3 events, if one includes categories of GI hemorrhage, Hematemesis, and Melena). In the pulmonary system, 'Respiratory insufficiency' was the main contributor to the difference in the 2 arms (11 events versus 1 event).

Treatment-Related Adverse Experiences

Investigator events attributed to treatment were more frequent on the PDT , 66% (73/110) , vs the YAG arm 37% (40/108) with p = 0.003. However, life-threatening or severe events attributed to treatment were similar on the 2 arms (19% for PDT versus 18% for YAG). These data are summarized in the sponsor's table 13I:

Table 13l. Number (Percentage) of Treated Patients Reporting at Least One Treatment-Related Adverse Event, by Body System, Individual Adverse Experience Within Body System and Treatment Group: Treatment-Related Events for Which the Treatment Difference in Incidence is at Least 5%, Based on All Treated Patients

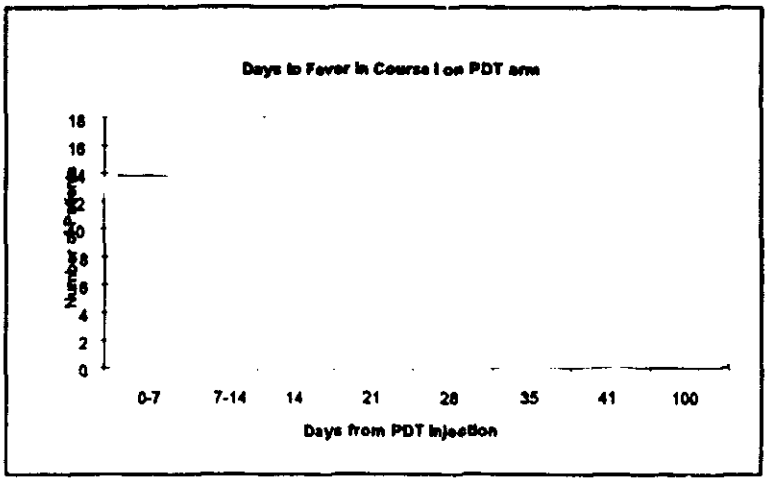
	PDT		Nd:YAG		Treatment Comparison P-value*
	No.	(%)	No.	(%)	
No. of Treated Pts.	110	(100)	108	(100)	
At Least One AE (any severity)	**73**	**(66.4)**	**40**	**(37.0)**	**p <0.01**
At Least One AE (severe or life-threatening)	21	(19.1)	19	(17.6)	
Type of Event					
All Skin and Appendages	22	(20.0)	0	(0.0)	p <0.01
Photosensitivity Reaction	**21**	**(19.1)**	**0**	**(0.0)**	**p <0.01**
All Gastrointestinal	37	(33.6)	25	(23.1)	p =0.13
Nausea	9	(8.2)	2	(1.9)	p =0.03
All Respiratory	26	(23.6)	14	(13.0)	p =0.06
Pleural Effusion	**11**	**(10.0)**	**2**	**(1.9)**	**p =0.01**
All Body as a Whole	36	(32.7)	18	(16.7)	p =0.01
Fever	**17**	**(15.5)**	**5**	**(4.6)**	**p <0.01**

* Treatment groups were compared with respect to the distribution of ordered severity scores (none, mild, moderate, severe, very severe/life-threatening) using a (two-sided) Wilcoxon test.

I have made bold the differences which are significant at p <= 0.01, which are Photosensitivity, Pleural effusion, and Fever.

The following is a histogram of time to fever on the PDT arm in course 1:

Bin	*Frequency*
0	18
7	4
14	0
21	0
28	1
35	1
41	4
100	0



The maximum grade of fever is tabulated below for these PDT pts. in course 1:

Maximum Grade	No. Pts.
1	20
2	7
3	2

Analysis of Incidence of adverse experiences by treatment group and by course:

The sponsor's table J (attached) reviews events according to Course number of therapy.

Reviewer comments:

One must consider that the meaning of a 'course' is defined differently for PDT versus YAG so that this alone could introduce bias in the listings of events per course.

Most of the findings which are significant in the study population as a whole, are noted in the first course; many of the trends also seen in course 2.

Comments on timing of AE's

The timing of several adverse reactions was examined by the reviewer. (Listings were sorted according to study day). Most esophageal strictures occurred day 40-70. Most esophageal ulcerative hemorrhage occurred at about 2 weeks. TE fistulas occurred

Table 13J. Number (Percentage) of Treated Patients Reporting at Least One Adverse Event, by Body System, Individual Adverse Experience within Body System, Course of Treatment and Treatment Group: Events Included in Table 13G

	ENTIRE STUDY PERIOD		COURSE 1		COURSE 2	
	PDT No. (%)	Nd:YAG No. (%)	PDT No. (%)	Nd:YAG No. (%)	PDT No. (%)	Nd:YAG No. (%)
No. of Treated Pts.	110 (100)	108 (100)	110 (100)	108 (100)	42 (100)	47 (100)
At Least One TAdverse Experience	101 (91.8)	88 (81.5)	96 (87.3)	82 (75.9)	40 (95.2)	27 (57.4)
Type of Event						
All Skin and Appendages	28 (25.5)	8 (7.4)	23 (20.9)	7 (6.5)	8 (19.0)	0 (0.0)
Photosensitivity Reaction	21 (19.1)	0 (0 0)	17 (15.5)	0 (0.0)	7 (16.7)	0 (0.0)
All Autonomic Nervous System	16 (14.5)	9 (8.3)	11 (10.0)	4 (3.7)	5 (11.9)*	5 (10.6)*
All Gastrointestinal	73 (66.4)	56 (51.9)	62 (56.4)	46 (42.6)	23 (54.8)	16 (34.0)
Abdominal Pain	21 (19.1)	12 (11.1)	15 (13.6)	9 (8.3)	8 (19.0)	3 (6.4)
Constipation	25 (22.7)	10 (9.3)	22 (20.0)	8 (7.4)	2 (4.8)*	2 (4.3)*
Nausea	23 (20.9)	16 (14.8)	15 (13.6)*	12 (11.1)*	9 (21.4)	3 (6.4)
Esophageal Ulceration	1 (0.9)	7 (6.5)	1 (0.9)*	5 (4.6)*	0 (0.0)*	2 (4.3)*
Vomiting	17 (15.5)	9 (8.3)	12 (10.9)	4 (3.7)	5 (11.9)*	4 (8.5)*
All Metabolic & Nutritional	18 (16.4)	10 (9.3)	14 (12.7)	7 (6.5)	4 (9.5)*	3 (6.4)*
Weight Decrease	8 (7.3)	2 (1.9)	7 (6.4)	1 (0.9)	1 (2.4)*	1 (2.1)*
All Myo-, Endo-, Pericardial & Valve	6 (5.5)	0 (0.0)	4 (3.6)*	0 (0.0)*	1 (2.4)*	0 (0.0)*
All Heart Rate/Rhythm	18 (16.4)	12 (11.1)	15 (13.6)	5 (4.6)	2 (4.8)*	4 (8.5)*

* Difference between the groups is less than 5%, but values are included for completeness.

Reference: Appendix X.D

Table 13J Cont'd: Number (Percentage) of Treated Patients Reporting at Least One Adverse Event, by Body System, Individual Adverse Experience within Body System, Course of Treatment and Treatment Group: Events Included in Table 13G

	ENTIRE STUDY PERIOD		COURSE 1		COURSE 2	
	PDT	Nd:YAG	PDT	Nd:YAG	PDT	Nd:YAG
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
All Respiratory	68 (61.8)	44 (40.7)	55 (50.0)	34 (31.5)	18 (42.9)	11 (23.4)
Pleural Effusion	31 (28.2)	6 (5.6)	23 (20.9)	4 (3.7)	8 (19.0)	2 (4.3)
Respiratory Insufficiency	11 (10.0)	1 (0.9)	10 (9.1)	1 (0.9)	1 (2.4)*	0 (0.0)*
Pharyngitis	10 (9.1)	4 (3.7)	7 (6.4)	1 (0.9)	2 (4.8)*	2 (4.3)*
All Red Blood Cell	29 (26.4)	13 (12.0)	21 (19.1)	8 (7.4)	5 (11.9)*	6 (12.8)*
Anemia	29 (26.4)	13 (12.0)	21 (19.1)	8 (7.4)	5 (11.9)*	6 (12.8)*
All Urinary	16 (14.5)	9 (8.3)	13 (11.8)	7 (6.5)	2 (4.8)*	2 (4.3)*
All Body as a Whole	75 (68.2)	58 (53.7)	66 (60.0)	44 (40.7)	25 (59.5)	17 (36.2)
Fever	36 (32.7)	11 (10.2)	29 (26.4)	8 (7.4)	11 (26.2)	1 (2.1)
Edema Generalized	8 (7.3)	2 (1.9)	4 (3.6)*	1 (0.9)*	2 (4.8)*	1 (2.1)*
All Resistance Mechanism	17 (15.5)	7 (6.5)	15 (13.6)	6 (5.6)	1 (2.4)*	0 (0.0)*

704 th

* Difference between the groups is less than 5%, but values are included for completeness.

Reference: Appendix X.D

over a spectrum of time, but were usually after 30 days. Dyspnea occurred at a variety of times; grade III on d 20 and d 40, grade II occurred often in weeks 1 and 2. The 30 instances of pleural effusion on the PDT arm had a median time of 8 days to occurrence.

Ophthalmic events:

The 3 patients with ophthalmic events are listed in the appendix (Pt and . The 2 grade 3 events are in patient Patient had ophthalmic metastases.

Patient had acute glaucoma. The case report form shows that it occurred no more than 1 day after laser application for PDT in course 2 (Laser date 2/13/91, eye pain and blurred vision 2/14/91). The following is the investigator's note from 2/14/91:

> "Pt. developed acute loss of vision following laser Rx. Dx= optic neuritis, rapidly ???? ??? and acute glaucoma-all occurring together-"

In another place on the case report form the event was described as eye pain and optic nerve congestion. It apparently responded to pharmacologic therapy for glaucoma.

Adverse experiences according to Formulation of Photofrin used:

The formulation of Photofrin was changed during the study so that the first 43 patients on the PDT arm received a frozen formulation and the last 67 received the lyophilized preparation. Table 13 K (attached) from the submission summarizes the sponsor's analysis.

The following text is from the sponsor's analysis of adverse reactions versus formulation (V 1.33 p 218):

"13.3.5 Adverse Experiences by Preparation of PHOTOFRIN® for the PDT Treated Group During the First Course of Treatment

Sixty-one percent (67/110) of patients treated with PHOTOFRIN® received the lyophilized preparation for their first injection of PHOTOFRIN®. (Table 13K and Data Display Table 13.3.5.1.) Ninety-six percent (64/67) experienced at least one adverse experience compared to 74% (32/43) of PDT-treated patients treated with the frozen formulation for their first injection. Forty-eight percent (32/67) of patients receiving the lyophilized preparation experienced at least one adverse experience which was rated severe or life-threatening by the Investigator compared to 28% (12/43) of patients receiving the frozen preparation (Data Display Table 13.3.5.1).

Table 13K. Number (Percentage) of PDT-Treated Patients Reporting at Least One Adverse Event During the First Course by Body System, Individual Adverse Experience within Body System, and Formulation of PHOTOFRIN®: Events for Which the Formulation Difference in Incidence is at Least 5%

	Frozen PHOTOFRIN® No.	(%)	Lyophilized PHOTOFRIN® No.	(%)
No. of PDT-Treated Pts.	43	(100)	67	(100)
At Least One Adverse Experience	32	(74.4)	64	(95.5)
Type of Event				
All Skin and Appendages	7	(16.3)	16	(23.9)
All Central Nervous System	1	(2.3)	10	(14.9)
All Psychiatric*	9	(20.9)	17	(25.4)
Anorexia*	0	(0.0)	4	(6.0)
Anxiety*	0	(0.0)	5	(7.5)
Insomnia	6	(14.0)	5	(7.5)
All Gastrointestinal	17	(39.5)	45	(67.2)
Abdominal Pain	3	(7.0)	12	(17.9)
Constipation	6	(14.0)	16	(23.9)
Diarrhea	5	(11.6)	2	(3.0)
Dysphagia	2	(4.7)	7	(10.4)
Hematemesis	1	(2.3)	7	(10.4)
Melena	0	(0.0)	4	(6.0)
Intestinal Stenosis	0	(0.0)	6	(9.0)
Nausea	2	(4.7)	13	(19.4)
Esophageal Ulceration Hemorrhage	0	(0.0)	5	(7.5)
Vomiting	2	(4.7)	10	(14.9)
All Metabolic & Nutritional	2	(4.7)	12	(17.9)
Weight Decrease	0	(0.0)	7	(10.4)
All Heart Rate/Rhythm	4	(9.3)	11	(16.4)
Fibrillation Atrial	1	(2.3)	5	(7.5)
All Respiratory	17	(39.5)	38	(56.7)
Coughing	0	(0.0)	4	(6.0)
Dyspnea	2	(4.7)	14	(20.9)
Pleural Effusion	3	(7.0)	20	(29.9)
Pneumonia	3	(7.0)	10	(14.9)
All Red Blood Cell	2	(4.7)	19	(28.4)
Anemia	2	(4.7)	19	(28.4)
All Body as a Whole	24	(55.8)	42	(62.7)
Back Pain	0	(0.0)	5	(7.5)
Surgical Complication	0	(0.0)	4	(6.0)

* Formulation difference is less than 5% for this body system category, but the difference is greater than 5% for the individual adverse experiences.

References: Appendices VIII.C, X.D

The incidence of adverse events reported in eight body system categories, "All Gastrointestinal", "All Body as a Whole", "All Respiratory", "All Red Blood Cell", "All Skin and Appendages", "All Metabolic and Nutritional", "All Heart Rate/Rhythm", and "All Central Nervous System", and 20 individual adverse experiences, anemia, pleural effusion, constipation, nausea, abdominal pain, dyspnea, esophageal ulceration hemorrhage, hematemesis, melena, pneumonia, intestinal stenosis, vomiting, atrial fibrillation, dysphagia, weight decrease, anorexia, back pain, anxiety, coughing, and surgical complication, was at least five percent greater for the lyophilized formulation. The incidence of two individual adverse experiences, insomnia and diarrhea, was approximately five percent greater for patients receiving the frozen formulation of PHOTOFRIN®."

Reviewer comments:

A problem with this analysis is that it is confounded by time. Early patients may have been treated by more experienced investigators, early data collection may not have been as complete, populations of patients may have changed, etc.

Reviewer analysis of formulation issue:

The following analyses were done independent of the sponsor's analysis. Patients were divided according to whether they were randomized before or after the date that the formulation amendment was submitted to the protocol (1/10/90). This is slightly different from the sponsor's analysis which used formulation actually given. The patients differing in these analysis are the following:

PT	DRUG*	RANDATE
	2	11/6/89
	2	12/1/89
	2	10/5/89
	2	10/5/89
	2	12/14/89
	0	2/7/90
	0	4/10/90
	0	1/29/90
	0	3/22/90
	0	3/29/90

*Drug assignment according to PDT data base, 2=lyophilized, 0=frozen.

This analysis by date of randomization allows for determining concurrent control groups of randomized patients on the YAG arm. Changes associated with time rather than treatment might be expected to manifest themselves in both arms.

The following table represents adverse events in all patients so divided by date of randomization:(before or after 1/10/90), whether or not treatment or drug was given. In each arm there were 77 patients after 1/10/90 and 44 patients before that date. The ratio of patients after/before was 1.88. Therefore a ratio of events greater than 1.88 represents an increase in average frequency per patient. The table demonstrates that average frequency of adverse event increased on the PDT arm (r=2.3) while it decreased on the YAG arm (r=1.3). Number of Patients with at least one event did not change as significantly (r= 2.03 and r=1.76). The frequency of grade 3 or 4 events did increase (r=2.55) on the photofrin arm, whereas the frequency of grade 4 events alone actually decreased slightly on both arms (1.54 and 1.29).

		PDT			YAG	
	Before*	After	ratio (a/b)	Before*	After	ratio (a/b)
Total Patients:	41	77	**1.88**	41	77	**1.88**
# Adverse events	226	528	2.34	207	267	1.29
# Pts with AE	34	69	2.03	33	58	1.76
AE events Gr 3&4	42	107	2.55	37	60	1.62
# Patients	16	42	2.63	19	31	1.63
AE events Gr 3&4	21	31	1.48	8	14	1.75
# Patients	13	20	1.54	7	9	1.29

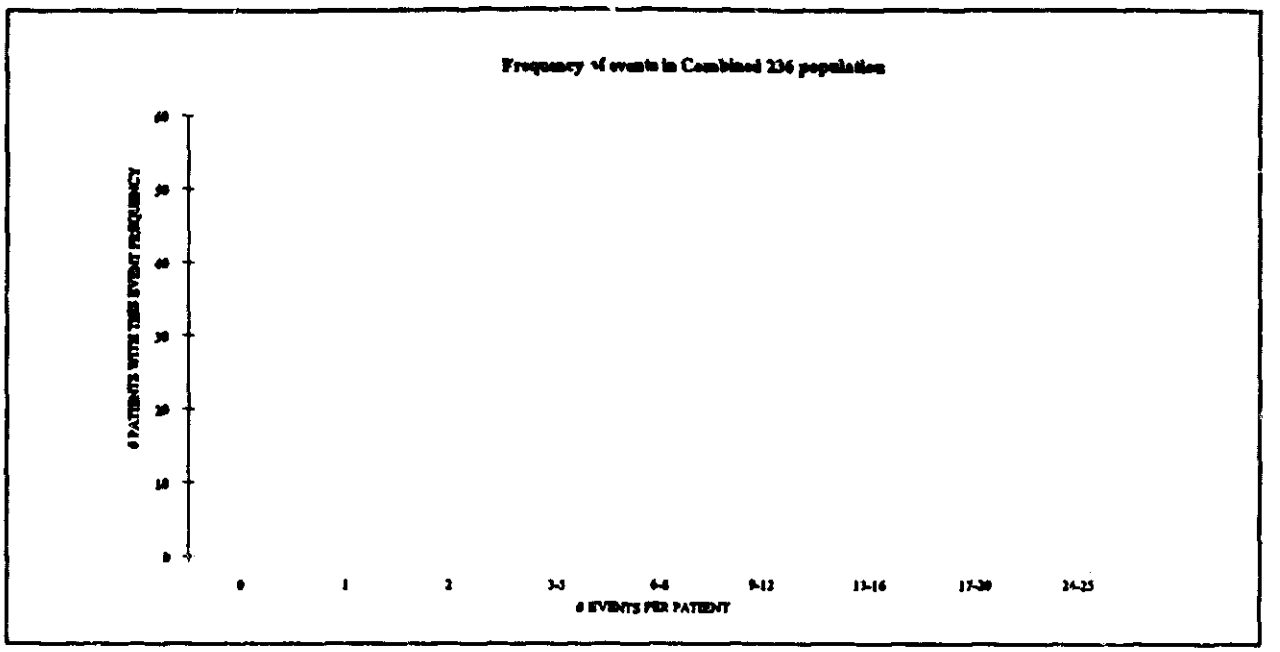
*Randomized before 1/10/90 (date of Protocol amendment for formulation change).

The increase in event rate can be viewed in 2X2 tables:

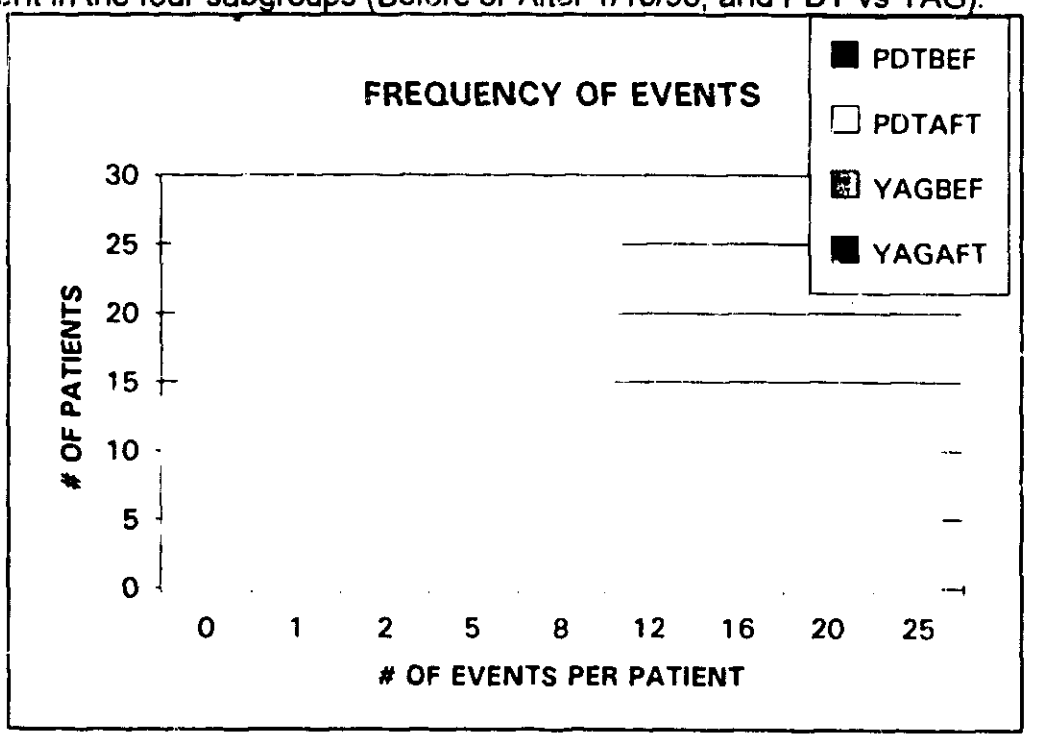
#AE'S			
	BEFORE	AFTER	TOTAL
PDT	226	529	755
YAG	208	267	475
TOTAL	434	796	1230

#PTS WITH AEs			
	BEFORE	AFTER	TOTAL
PDT	34	69	103
YAG	33	58	91
TOTAL	67	127	194

The above analyses suggested that perhaps a few patients in the 'After-PDT' group were responsible for the increase in total events. The following analyses examine the number of events per patient in the overall popuiation and in the 4 subgroups:



This shows that most patients in the combined population had less than 5 reported events. To compare whether the increase in events in the'PDT-After' group was due to a few patients, each with many events, or whether it was due to a more broad distribution of events, the following analysis views the frequency distribution of events per patient in the four subgroups (Before or After 1/10/90; and PDT vs YAG).



It appears from this analysis that no special pattern of events occurred in the 'PDT-

after' group: that the increase frequency of reported events seems distributed among many patients.

The events with an increased frequency are noted in the following table. Event rates are normalized to 100 patients per arm (multiplied by factors of 2.4 or 1.3). Categories were selected for the table if normalized rate after 1/10/90 was more than 5% and if ratio (after:before) was more than 2.

Number of AE's with PDT Before and After Lyophilized Formulation*:

CAT	AE	nbefore	nafter	Ratio
AUTONOMIC NERVOUS SYSTEM	HYPERTENSION	2.4	6.5	2.7
BODY AS A WHOLE	ASTHENIA	2.4	5.2	2.1
BODY AS A WHOLE	BACK PAIN	2.4	9.1	3.7
GASTROINTESTINAL	ABDOMINAL PAIN	9.8	29.9	3.1
GASTROINTESTINAL	MELAENA	2.4	5.2	2.1
HEART RATE/RHYTHM	FIBRILLATION ATRIAL	2.4	14.3	5.9
METABOLIC & NUTRITIONAL	WEIGHT DECREASE	2.4	9.1	3.7
RED BLOOD CELL	ANAEMIA	9.8	33.8	3.5
RESPIRATORY	DYSPNOEA*	7.3	24.7	3.4
RESPIRATORY	PHARYNCITIS	4.9	10.4	2.1
RESPIRATORY	PLEURAL EFFUSION	14.6	35.1	2.4

*Randomized before or after 1/10/90, normalized to 100 patients per group.

Similarly the following analysis considers numbers of patients with a given adverse reaction rather than number of events:

Number of Patients with PDT AES Before and After Lyophilized Formulation:*

CAT	AE	BEFORE	AFTER	nBefore	nAfter	n(ratio)
AUTONOMIC NERVOUS SYSTEM	HYPERTENSION	1	5	2.4	6.5	2.7
BODY AS A WHOLE	ASTHENIA	1	4	2.4	5.2	2.1
BODY AS A WHOLE	BACK PAIN	1	6	2.4	7.8	3.2
GASTROINTESTINAL	ABDOMINAL PAIN	4	17	9.8	22.1	2.3
GASTROINTESTINAL	MELAENA	1	4	2.4	5.2	2.1
GASTROINTESTINAL	OESOPHAGEAL ULCERATION HAEMORRHAG	1	6	2.4	7.8	3.2
HEART RATE/RHYTHM	FIBRILLATION ATRIAL	1	8	2.4	10.4	4.3
METABOLIC & NUTRITIONAL	WEIGHT DECREASE	1	7	2.4	9.1	3.7
RED BLOOD CELL	ANAEMIA	4	25	9.8	32.5	3.3
RESPIRATORY	DYSPNOEA	3	17	7.3	22.1	3
RESPIRATORY	PHARYNGITIS	2	8	4.9	10.4	2.1
RESPIRATORY	PLEURAL EFFUSION	6	25	14.6	32.5	2.2
BODY AS A WHOLE	SURGICAL COMPLICATION		4	0	5.2	
CENTRAL NERVOUS SYSTEM	HEADACHE		3	0	3.9	
GASTROINTESTINAL	INTESTINAL STENOSIS		7	0	9.1	
PSYCHIATRIC	ANOREXIA		6	0	7.8	
PSYCHIATRIC	ANXIETY		5	0	6.5	
PSYCHIATRIC	CONFUSION		6	0	7.8	
RESPIRATORY	COUGHING		4	0	5.2	
URINARY	URINARY RETENTION		3	0	3.9	
VISION	VISION ABNORMAL		3	0	3.9	

*Groups selected for Nafter > 3 and R >2 or Nafter >2 and Nbefore = 0.

Reviewer comments:

These analyses convincingly demonstrate an increased rate of adverse event reporting in the PDT arm after the date of the formulation-change amendment of 1/10/90. The fact that the event rate did not increase on the YAG arm over the same period of time suggests that something intrinsic to the PDT arm changed. Formulation is one possibility; other possibilities include experience of investigators at delivering PDT and method of event monitoring.

Review of selected AEs and AE texts:

Data from several adverse reactions which were of special interest or were more common on the PDT arm were more closely examined. The distribution of PDT patients according to worst grade is displayed for these selected AE's:

		GRADE OF EVENT				
CAT	**AE**	**1**	**2**	**3**	**4**	**Total**
AUTONOMIC N S	GLAUCOMA			1		1
BODY AS A WHOLE	BACK PAIN	3	2	1		6
BODY AS A WHOLE	FEVER	23	9	3		35
BODY AS A WHOLE	SURGICAL COMPLICATION	2	2			4
GASTROINTESTINAL	ABDOMINAL PAIN	5	11	5		21
GASTROINTESTINAL	GI HAEMORRHAGE		2		3	5
GASTROINTESTINAL	HAEMATEMESIS	6	1	2	3	12
GASTROINTESTINAL	HICCUP	1				1
GASTROINTESTINAL	INTESTINAL STENOSIS	2	4	1		7
GASTROINTESTINAL	OESOPHAGEAL STRICTURE		4	2		6
GASTROINTESTINAL	OESOPHAGEAL ULCERATION		1			1
GASTROINTESTINAL	OESOPHAGEAL ULCERATION HAEMORRHAGE	3	2	1	1	7
GASTROINTESTINAL	OESOPHAGITIS	2	1	1		4
HEART RATE/RHYTHM	FIBRILLATION ATRIAL	2	3	2	2	9
RED BLOOD CELL	ANAEMIA	9	14	5	1	29
RESPIRATORY	DYSPNOEA	5	13	2		20
RESPIRATORY	PLEURAL EFFUSION	3	15	10	3	31
RESPIRATORY	PNEUMONIA	7	3	3	6	19
RESPIRATORY	RESPIRATORY INSUFFICIENCY				12	12
RESPIRATORY	TRACHEO-OESOPHAGEAL FISTULA		1	4	6	11
SKIN AND APPENDAGES	PHOTOSENSITIVITY REACTION	15	6			21
VISION	EYE PAIN			1		1
VISION	PHOTOPHOBIA	1				1
VISION	VISION ABNORMAL	1		2		3

Concomitant medications:

The sponsor compared concomitant medication use on the 2 arms. The following is table 13 L from the submission. I have added Asterisks and numbers indicating differences between the 2 arms that are 5% or greater. This includes Analgesic (14), Other(15), Antibiotic (13), Cardiac (8) and anti-inflammatory.

Table13L. Number (Percentage) of Treated Patients Requiring Concomitant Medications During the Entire Study Period, by Major Category of Medication and

Treatment Group	PDT		Nd:YAG		
	No.	(%)	No.	(%)	
No. Treated	110	(100.0)	108	(100.0)	
With at Least One Concomitant Medication	105	(95.5)	101	(93.5)	
Medication Category					
Analgesic*	75	(68.2)	59	(54.6)	*14
Gastrointestinal	74	(67.3)	75	(69.4)	
Other*	70	(63.6)	47	(43.5)	*15
Antibiotic*	63	(57.3)	43	(39.8)	*13
Central Nervous System Meds	42	(38.2)	40	(37.0)	
Cardiac (Non-Anti-Arrhythmic)*	39	(35.5)	30	(27.8)	*8
Respiratory Function*	24	(21.8)	16	(14.8)	*7
Cardiac (Anti-Arrhythmic)	23	(20.9)	23	(21.3)	
Anti-Hypertensive	23	(20.9)	19	(17.6)	
Antiemetic*	22	(20.0)	15	(13.9)	*6
Anti-Inflammatory	20	(18.2)	15	(13.9)	*7
Endocrine	17	(15.5)	13	(12.0)	
Parasympathetic (Anticholinergic)	2	(1.8)	3	(2.8)	

*% Difference PDT-Yag is at least 5%.

Similarly the following is an excerpt from the sponsor's table 13 M, of medications required during the first 60 days of course 1. This analysis is likely to reflect the impact of therapy. It shows an even greater difference between arm in medication use. The incidence of medication use was at least 5% higher in the PDT arm in the following categories: Analgesic, GI, Antibiotic, Other, Cardiac (non-anti-arrhythmic ,Respiratory function, Cardiac (anti-arrhythmic), and Antiemetic.

Table13M

. Number (Percentage) of Treated Patients Requiring Concomitant Medications Within 60 Days After the Start of the First Treatment Course, by Major Category of Medication and Treatment Group

	PDT		Nd:YAG		
	No.	(%)	No.	(%)	
No. Treated	110	(100.0)	108	(100.0)	
With at Least One Concomitant Medication	86	(78.2)	63	(58.3)	*20
Medication Category					
Analgesic*	48	(43.6)	31	(28.7)	*15
Gastrointestinal*	47	(42.7)	33	(30.6)	*12
Antibiotic*	39	(35.5)	23	(21.3)	*14
Other*	38	(34.5)	18	(16.7)	*18
Cardiac (Non-Anti-Arrhythmic)*	19	(17.3)	5	(4.6)	*13
Central Nervous System Meds	17	(15.5)	12	(11.1)	
Respiratory Function*	15	(13.6)	5	(4.6)	*9
Cardiac (Anti-Arrhythmic)*	14	(12.7)	7	(6.5)	*6
Anti-Inflammatory	12	(10.9)	7	(6.5)	
Antiemetic*	11	(10.0)	5	(4.6)	*5
Endocrine	5	(4.5)	5	(4.6)	
Anti-Hypertensive	3	(2.7)	3	(2.8)	
Parasympathetic (Anticholinergic)	0	(0.0)	1	(0.9)	

* % Difference PDT-Yag is at least 5%.

Reviewer comments:

These analyses of medication use verify the findings of increase in adverse reactions on the PDT arm. These medications would appear to be used in dealing with such adverse reactions. Such medications appear to have been used to palliate such reactions.

6.1.5.3 Clinical laboratory abnormalities:

The sponsor analyzed laboratory data according to WHO criteria which are defined in figure 5 from the submission (attached).

Reviewer comments:

In section 13.5 I think the sponsor does an inadequate job of discussing lab abnormalities. The tables (13 N to 13 W) are nicely detailed, but no statistical analyses are done and there is no real explanation of individual cases or attempt to assign or rule out causality. The sponsor should perform statistical analyses and should address any differences that are significant on the 2 arms.

Renal function:

10 PDT patients with normal baseline creatinine had a followup creatinine elevation of at least grade I degree compared to 6 YAG patients. There was one grade II elevation and one grade III elevation on the YAG arm; there was one grade II elevation and one grade III elevation on the PDT arm.

Liver function:

The following is taken from the sponsor's analysis of alkaline phosphatase values in table 13P. It represents patients with baseline Grade 0 alkaline phosphatase on the 2 arms.

Alkaline Phosphatase:

Grade:	0	1	2	3	4	Unknown	Total
PDT	58	9	4	4	0	5	80
YAG	50	14	2	2	0	14	81

Of about 90 patients with normal baseline SCOT on each arm, 22 PDT patients and 17 Yag patients had a followup SCOT of Grade I or higher. The following data is from the sponsor's table 13R:

SCOT

Grade:	0	1	2	3	4	Unknown	Total
PDT	64	14	7	1	o	4	90
YAG	64	13	3	0	1	13	94

About 100 patients in each arm had normal baseline bilirubin. Followup data for these patients is from the sponsor's table 13T:

Bilirubin:

Grade:	0	1	2	3	4	Unknown	Total
PDT	81	6	1	3	1	7	99
YAG	76	4	1	0	0	15	96

Data from patients with grade III and IV elevations of alkaline phosphatase or bilirubin were examined in more detail. Cross-tabulations of pertinent data from these patients can be found in the appendix of the review. Clinical Capsules and investigator comments, and in most cases, case report forms were reviewed.

Notes on selected patients follow:

This patient had an acute abdomen and was operated on for necrotic gallbladder 1 wk after treatment. She died on day 17 with death attributed to CHF.

This patient had normal Alk phos at entry. On day 9 alk phos was 3.5 times upper limit of normal, and on day 28 it was 3.9X nl. On day 28 patient had UTI and hypercalcemia. The patient died on day 56 from disease progression.

This patient had an increase in alkaline phosphatase on day 83 during a complicated clinical course related to an esophago-pleural fistula.

This patient's marked elevation of LFTs was from tumor metastatic to liver.

This patient had elevation of LFT's noted on day 11 of course 3. This progressed and CRF notes patient had Flank Pain, increased liver enzymes and edema on 7/21/90.

This patient had elevation of alkaline phosphatase to 1.3 X nl on day 9 with progressive elevation on day 29, 51, and 75 (last value 5.9 X nl). Bilirubin was about 6 X nl on days 65 and 75. Patient had pleural effusions tapped. He died on day on day 175. Etiology of increased LFTs is unclear.

This patient had increased SCOT and alkaline phosphatase first documented on day 36 of course 1 and then on day 7 of course 2. CRF mentioned hepatomegaly which was presumed to be from metastatic disease to liver. Patient was severely debilitated and was assumed to die of progressive disease.

This patients elevation of alk phos and bilirubin on day 9 resolved with bypass of tumor obstructing biliary system.

Reviewer comments:

Given the clinical condition of these patients one cannot determine whether PDT was responsible for liver function abnormalities in many of these patients. Serial followup of liver function tests in another, less ill, population will be needed to rule out this possibility.

Bone marrow function:

Hemoglobin and Platelet data in patients with baseline normal values is taken from the sponsor's tables 13 v and 13 w. Numbers of patients are listed according to WHO grade.

Hemoglobin:

Grade:	0	1	2	3	4	Unknown	Total
PDT	40	22	10	2	2	2	78
YAG	48	15	10	4	3	5	85

Platelets:

Grade:	0	1	2	3	4	Unknown	Total
PDT	92	0	3	0	1	4	100
YAG	86	1	2	1	0	11	101

Reviewer comments:

In searching the data base Pt. was found to have the grade IV thrombocytopenia. The patient had a plt count of 7000 on 3/4/91 (day 56). The patient went offstudy for progression went on to receive Yag therapy. This CRF was not submitted, and will be requested.

Pt . on day 69 of course 4, had plt count go from 300k several days before to zero. The patient was admitted for pneumonia, and died 10 days later. This thrombocytopenia was probably secondary to pneumonia and sepsis, and/or antibiotic reaction; it seems very unlikely that it was related to PDT treatment.

6.1.6 Applicant's Conclusions (excerpts from P19 Study Report)

The Study Report ends with 20 pages of comprehensive summary and conclusions. The following excerpts seem most pertinent:

"There are four major efficacy endpoints. Change in dysphagia grade compared to baseline, describes the degree of improvement in the major symptom requiring palliation in this patient population. Time to treatment failure describes the length of time that a patient remains on treatment prior to therapeutic failure. In this analysis, failure reasons are both palliative and non-palliative. This allows for a minimum of censored evaluations, however, it is not a pure description of the duration of time a patient may actually be palliated. Time to palliation failure was developed as a time dependent efficacy parameter attempting to measure only the duration of the palliative effect of PDT. It was defined as the interval from treatment start until the first evidence of worsening dysphagia, treatment related toxicity, failure to palliate, retreatment, or dilation of the esophagus at any point after the Week 1 assessments. This was distinct from time to treatment failure, where progressive disease and death, not necessarily failure of palliation, were among the major reasons for treatment failure. Thus, for example, in the analysis of time to palliation failure a patient with no evidence of progressive dysphagia who dies or is removed from study due to disease progression is censored.

The fourth major efficacy endpoint, objective response, provides an assessment of the

efficacy with which the treatment debulked tumor tissue.

Minor efficacy endpoints include change from baseline in KPS and body weight and survival.

Within each course of therapy, discussions involving comparisons of the two randomization groups are restricted to the Week 1 and Month 1 visits, since the number of patients with data available for analysis beyond the Month 1 visit, within any course of therapy, is too small.

At baseline, the average dysphagia grade for the two treatment groups was 3 on a scale of 1 to 5. During the first course of therapy, the average improvement in dysphagia was similar for the two groups at both the Week 1 and Month 1 visits, resulting in an overall improvement to a dysphagia grade of 2 in both treatment groups. Similar proportions of patients in the two groups were without evidence of improvement."

"Results of the analysis of time to treatment failure over the first course of therapy were similar for the two groups. The median time to treatment failure over the first course of therapy was 35 days for PDT and 40 days for Nd:YAG. The risk of treatment failure was 0.99 for Nd:YAG patients compared with PDT patients; the 95% confidence interval for the relative risk ranged from 0.76 to 1.29. The predominant reasons for treatment failure were worsening dysphagia, progressive disease, death, and dilation among PDT patients, and progressive disease, worsening dysphagia, and patient requests withdrawal from treatment among Nd:YAG patients. As discussed previously, time to palliation failure was developed as a time dependent efficacy parameter attempting to measure the duration of the palliative effects of the two treatments in relieving malignant dysphagia. The median time to palliation failure for the first course of treatment, was 34 days for PDT patients and 42 days for Nd:YAG patients. The risk of palliative failure was 0.82 for Nd:YAG patients compared with PDT patients; the 95% confidence interval for the relative risk ranged from 0.60 to 1.10. Eighty percent of PDT patients and 70% of Nd:YAG patients failed during the first course of therapy. The reasons for failure were similar for both randomization groups."

"With regard to the length of tumor at baseline, for tumors over 10 cm in length, PDT treated patients had superior response rates compared to Nd:YAG treated patients at both the Week 1 and Month 1 assessments. Response rates for the small and

intermediate tumor lengths were similar at the Week 1 assessment. At the Month 1 assessment, PDT treated patients had superior response rates for tumors less than 5 cm in length, while Nd:YAG treated patients had superior response rates for tumors 6 to 9 cm in length. Among patients who had not received any prior therapy for esophageal cancer, PDT tended to result in higher response rates at the Month 1 evaluation while among those who had received prior therapy for esophageal carcinoma, PDT resulted in higher response rates at both Week 1 and Month 1.

Similar to the observation for dysphagia grade, response rates tended to vary from site to site with no consistent trend. When pooled data from sites enrolling 14 or more patients were compared, the objective response rate for the two groups was similar at the Week 1 assessment, but the response rate for PDT was superior at the Month 1 assessment. For sites enrolling fewer than 9 patients, response rates for PDT and Nd:YAG were similar at both the Week 1 and Month 1 assessments.

In summary, based on objective response criteria as defined for this study, it appears that PDT accomplishes comparable debulking of tumor with a potentially favorable duration of this effect as evidenced by a higher Month 1 response rate for PDT patients over Nd:YAG patients. Moreover, in a number of patient subgroups, the ability of PDT to debulk tumor may be advantageous, particularly when treating tumors at fixed points in the esophagus, namely in the cervical esophagus and at the gastroesophageal junction, which are somewhat more technically demanding procedures for the Nd:YAG laser.

The results with regard to differences in objective response rates between the two groups must be interpreted with some caution. In the assessment of the overall response rate and the assessment of response rate in the various subgroups, there are a large number of missing evaluations, particularly for the Nd:YAG treated patients. Indeed, a larger percentage of patients had missing evaluations for objective response compared to missing evaluations of dysphagia in both randomization groups at both the Week 1 and Month 1 evaluation points.

The criteria used to define a response are based on percentage increases in esophageal luminal diameter and not on absolute increase in luminal diameter measurements. In addition, the response criteria fail to take into account changes in the length of the tumor being treated. Thus, the true ability of the two therapies to debulk tumor is probably suboptimally measured. Finally, superiority in response rate does not correlate with improvement in dysphagia when comparing PDT to Nd:YAG laser therapy in the overall study population and in the various subgroups analyzed."

"Safety results are reported for all 218 treated patients (110 PDT; 108 Nd:YAG). As expected, given the palliative nature of the two therapies, the majority (87% PDT; 86% Nd:YAG) of patients in both arms of the study have died. The causes of death and the distribution of time to death from randomization appear similar for the two treatment groups. Similar numbers of patients in both groups died within 30 days of a treatment procedure, in either the first or second course of treatment.

Six deaths were considered treatment related by the Investigator among the PDT treated patients compared to none among the Nd:YAG treated patients. The cause of death in these six cases was progressive disease in one patient, infection in two patients, esophageal or gastrointestinal hemorrhage in one patient, congestive heart failure in one patient and tracheo-esophageal fistula in one patient. While it is impossible to dismiss the attribution of death to PDT in these 6 cases, it must be pointed out that only two of the causes of death are unique to PDT, hemorrhage and tracheo-esophageal fistula. Hemorrhage may indeed be a risk of PDT since, unlike Nd:YAG therapy, treatment with PDT does not induce immediate coagulative necrosis. Fistulae, on the other hand, appear to occur with equal frequency in Nd:YAG or PDT treated patients on this study.

Similar percentages of treated patients in both groups were removed from the study secondary to adverse events (12% PDT; 16% Nd:YAG). The predominant adverse event resulting in removal from study in both groups was fistula formation. Reasons for removal from study which were unique to the Nd:YAG group included esophageal perforation, a known complication of thermal ablation with the Nd:YAG laser, and stroke, a possible result of air emboli, described in the Nd:YAG literature in the palliative treatment of lung cancer[39]. Unique to PDT, laryngotracheal edema, is a potential sequela of post-treatment inflammatory response."

"The overall comparisons of adverse events between the two treatment groups consistently reveal both an excess total number and an excess of severe and life threatening adverse events among PDT treated patients. For a number of body system categories and individual adverse events, these differences are statistically significant.

In the overall analysis of adverse events there were a total of 11 body system categories where there was a > 5% difference in the incidence of adverse events amongst PDT treated patients compared to Nd:YAG treated patients. The majority of these differences are the result of an excess of mild and moderate adverse events, occurring in the first course of therapy, among the PDT treated patients. For certain adverse events, such as photosensitivity reactions, the difference between PDT and Nd:YAG was expected based on the nature of the therapy. Other events such as fever and pleural effusions may be the results of an inflammatory response resulting from PDT. Among the gastrointestinal adverse events, constipation appears to be

associated with an increased incidence of narcotic analgesic use amongst PDT treated patients. The majority of these events were self limited and their impact on the palliative ability of PDT is minimal.

However, there were several severe and life threatening adverse events unique to the two treatment groups which did impact on the palliative effect of the therapies. Among PDT treated patients, these included an excess of respiratory insufficiency, as well as severe and life threatening cardiac abnormalities, and severe and life threatening gastrointestinal bleeding. The cardiac and respiratory abnormalities may represent an as yet unreported locoregional toxicity of PDT. The excess of gastrointestinal bleeding, specifically gastrointestinal hemorrhage, hematemesis and melena, is potentially attributable to either the lack of immediate coagulative necrosis with PDT or, to a delay in the photodynamic effect causing erosion into blood vessels in the immediate vicinity of the treated tumor.

In the Nd:YAG treated patients, there was a greater incidence of esophageal perforation, an expected complication of Nd:YAG treatment, as well as a greater incidence of cerebrovascular accidents, potentially attributable to air emboli resulting from the Nd:YAG procedure. In addition, severe pain was reported more frequently in the Nd:YAG treated patients.

When only adverse events considered treatment related are considered, the overall incidence of treatment related adverse events was greater for the PDT treated patients (66% PDT; 37% Nd:YAG). Specific adverse events contributing to this imbalance include photosensitivity reactions, fever, pleural effusions and nausea. As in the overall analysis, the imbalance in incidence of treatment related adverse events is largely due to an excess of mild to moderate adverse events occurring amongst PDT treated patients during the first cycle of therapy."

"Within the PHOTOFRIN® treated group, the incidence and severity of adverse events was compared based on the formulation of PHOTOFRIN® received; frozen liquid or lyophilized. Both the overall incidence of adverse events and the incidence of severe and life threatening adverse events were greater for PDT patients treated with the lyophilized formulation. As the two formulations were used sequentially within the clinical trial, this result is no doubt confounded by a number of factors, such as, patient selection over time, and the addition of new investigational sites to the study following its' initiation. However, a possible difference in potency between the frozen liquid and lyophilized preparations of PHOTOFRIN® cannot be ruled out.

Concomitant medication usage in the two treatment groups was also assessed in terms of overall usage of concomitant medications and the use of concomitant medication beginning within 60 days of the start of the first course of treatment. While the

percentage of patients in both groups treated with concomitant medication is similar in the overall comparison, more PDT treated patients initiated concomitant medication within 60 days following the start of therapy. In general, the excess occurs in categories of medication which appear related to the treatment of adverse events.

An extensive evaluation of changes in laboratory parameters including renal function tests, liver function tests, and hematology tests is reported. There are no substantive differences between the treatment groups with regard to any of the above mentioned laboratory parameters.

In conclusion, Photodynamic Therapy with PHOTOFRIN® (porfimer sodium) is an active treatment for malignant dysphagia resulting from partially obstructing esophageal tumors, with a level of activity similar to the Nd:YAG laser. The safety profile of PDT for this indication may be a concern. Further refinement of light dosimetry and/or drug dose may ameliorate the adverse effect profile, particularly the mild to moderate locoregional toxicities observed with PDT. Like any surgical procedure, practitioner experience and patient selection play a role in outcome. Thus, it is likely that experienced clinicians, will over time, identify those patient subgroups at greatest risk for serious morbidity from PDT and further enhance the utility of this new palliative modality."

6.1.7 Reviewer Conclusions, Study P19

The sponsor presents results from a difficult randomized comparative multicenter trial performed over several years. The disease (esophageal cancer) is one in which doctors and patients have few effective therapeutic options. The important question to be asked of this trial, from a regulatory point of view, is whether evidence of efficacy significantly outweighs evidence of toxicity to suggest that the therapeutic ratio is favorable.

There are many problems with the efficacy endpoints and efficacy data. The time to event endpoints are complex, and include vague elements. Objective response definition was altered due to practical considerations. Followup data on all efficacy endpoints is inadequate, because of deaths and dropouts, to make any meaningful comparison between arms. However, within arm comparisons to baseline do suggest a favorable change in physical findings (lumenal diameter) and subjective findings (dysphagia grade) in about a third of the PDT patients. The clinical significance of this finding is difficult to assess, but review of the table in the efficacy section of this review may be of some assistance with this task(page 57) Analyses do suggest a correlation between the subjective (dysphagia grade) and physical (luminal diameter) scales.

Toxicity observed on the PDT arm is of concern. Many analyses, including adverse events, deaths onstudy, adverse events attributed to study treatment, and medication use suggest that patients on the PDT arm experienced considerably more toxicity. A couple of adverse events were unique to PDT: one patient developed symptoms leading to a diagnosis of acute glaucoma within a day of laser application for PDT and 4 patients with proximal tumors developed signs or symptoms of laryngeal edema (one requiring emergency tracheostomy).

In my opinion results of study P19 do not suggest that PDT, as administered in this study, has an acceptable therapeutic ratio for patients with partially obstructing esophageal cancer. It will be important to seek the Oncology Drugs Advisory Committee's opinion about the balance between efficacy and safety demonstrated in this study.

Study P20 in 17 patients with completely obstructing esophageal cancer is still under review. Another issue still under review is the impact of manufacturing changes occurring late in the course of the P19 study. A review of these issues will be contained in Medical Officer Review #2.

cc: Orig NDA
DIV file
HFD-150, Williams, Zimmerman (2)
HFD-340 G Turner
HFZ-410 R Felton

Grant Williams MD
8-17-94

9 Burke MD
9/13/94

APPENDIX III

TOXICITY GRADING

	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Very Severe)
Hematologic					
Hemoglobin (g/dl)	≥11.0	9.5 - 10.9	8.0 - 9.4	6.5 - 7.9	<6.5
Leukocytes ($1000/mm^3$)	≥4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	1.0
Granulocytes ($1000/mm^3$)	≥2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	<0.5
Platelets ($1000/mm^3$)	>100	75 - 99	50 - 74	25 - 49	<25
Hemorrhage	None	Petechiae	Mild blood loss	Gross blood loss	Debilitating blood loss
Gastrointestinal					
Bilirubin	≤1.25 x N[a]	1.26 - 2.5 x N[a]	2.6 - 5 x N[a]	5.1 - 10 x N[a]	>10 x N[a]
SGOT/SGPT	≤1.25 x N[a]	1.26 - 2.5 x N[a]	2.6 - 5 x N[a]	5.1 - 10 x N[a]	>10 x N[a]
Alkaline phosphatase	≤1.25 x N[a]	1.26 - 2.5 x N[a]	2.6 - 5 x N[a]	5.1 - 10 x N[a]	>10 x N[a]
Oral	No change	Soreness/ erythema	Erythema, ulcers; can eat solids	Ulcers; requires liquid diet only	Alimentation not possible
Nausea/vomiting	None	Nausea	Transient vomiting	Vomiting requiring therapy	Intractable vomiting
Diarrhea	None	Transient, <2 days	Tolerable, but >2 days	Intolerable, requiring therapy	Hemorrhagic dehydration
Mucositis	None	Mild	Moderate	Severe	Very severe

[a] N = upper limit of normal value of population under study.

PRB 8832001A3
03/08/89

Appendix I

APPENDIX III (Continued)

TOXICITY GRADING

	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Very Severe)
Renal, Bladder					
BUN or blood urea	≤1.25 x N[a]	1.26 - 2.5 x N[a]	2.6 - 5 x N[a]	5-10 x N[a]	>10 x N[a]
Creatinine	≤1.25 x N[a]	1.26 - 2.5 x N[a]	2.6 - 5 x N[a]	5-10 x N[a]	>10 x N[a]
Creatinine clearance	N[a]	0.75 - 0.99 x N[a]	0.50 - 0.74 x N[a]	0.25 - 0.49 x N[a]	<0.25 x N[a]
Proteinuria	None	1+, <0.3 g/dl	2 - 3+, 0.3 - 1.0 g/dl	4+, >1.0 g/dl	Nephrotic syndrome
Hematuria	None	Microscopic	Gross	Gross + clots	Obstructive uropathy
Dysuria	None	Mild dysuria or frequency, mild telangiectasis	Dysuria or freq. req. therapy, general telangiectasis	Hemorrhagic cystitis, bladder contracted to 100-150 cc capacity	Necrosis, bladder capacity <100 cc
Pulmonary					
Symptoms	None	Mild symptoms	Exertional dyspnea	Dyspnea at rest	Complete bed rest required
X-ray	Normal	Linear streaking	Bilateral infil., opacification <50% of lung volume	Opacification 50-75%	>75% Opacification
Function	Normal	25-50% decrease in Dco or VC	>50% decrease in Dco or VC	-	-

[a] N = upper limit of normal value of population under study.

PRB 8832B001A3
03/08/89

APPENDIX III (Continued)

TOXICITY GRADING

	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Very Severe)
Cardiac					
Rhythm	No change	Sinus tachycardia, >110 at rest	Unifocal PVC, atrial arrhythmia	Multifocal PVC	Ventricular tachycardia
Function	No change	Asymptomatic, but abnormal cardiac sign	Transient, symptomatic dysfunction; no therapy required	Symptomatic dysfunction responsive to therapy	Symptomatic dysfunction non-responsive to therapy
Pericarditis	None	Asymptomatic effusion	Symptomatic; no tap required	Tamponade; tap required	Tamponade; surgery required
Neurotoxicity					
Central	Normal	slight or transient uncoordination, dysdiadochokinesis, mild or transient alteration	Intention tremors, dysmetria, slurred speech, function substantially affected <50% decrease in baseline	Locomotor ataxia, >50% decrease in baseline function, convulsions	Brain necrosis, status epilepticus
Mental status	Alert	Transient lethargy	Somnolence <50% of waking hours	Somnolence >50% of waking hours	Coma
Peripheral	Normal	Mild weakness, mild paresthesia, decreased deep tendon reflexes, mild constipation	Moderate weakness, marked paresthesia, absent deep tendon reflexes, marked constipation	Severe weakness, disabling sensory loss, severe pain, obstipation, bladder dysfunction	Paralysis, obstipation requiring surgery

APPENDIX III (Continued)

TOXICITY GRADING

	Grade 0 (None)	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Very Severe)
Integument					
Cutaneous	No change	Erythema	Dry desquamation, vesiculation, pruritus	Moist desquamation, ulceration	Exfoliative dermatitis, necrosis req. surgical intervention
Hair	No change	Minimal hair loss	Moderate, patchy alopecia	Complete alopecia, but reversible	Non-reversible alopecia
Other					
Fever-Drug	None	Fever <38°C	Fever 38°C-40°C	Fever >40°C	Fever with hypotension
Allergic	None	Edema	Bronchospasm, no parenteral therapy needed	Bronchospasm, parenteral therapy required	Anaphylaxis
Infection (specify site)	None	Minor infection	Moderate infection	Major infection	Major infection with hypotension
Pain	None	Mild	Moderate	Severe	Intractable
Conjunctivitis	None	Discomfort, pain, photophobia, no therapy necessary	Discomfort, pain, photophobia, responsive to eyewashes and/or steroid drops	Discomfort, pain, photophobia, unresponsive to eyewashes and/or steroid drops	Significant visual impairment unrelated to pain, photophobia, corneal involvement, unresponsive to eyewashes and/or steroid drops
Other	None	Mild	Moderate	Severe	Very Severe

Adapted from WHO Recommendations for Grading of Acute and Subacute Toxicity

PRB 8932800IA3
03/08/89

Appendix 2

PDT patients removed from study for adverse events(comments on patients in table 13E after review of tabulations and narratives.)

Patient

This pt had laryngo-tracheal edema on day 3 of course 1, three and one half hours after laser therapy. Her tumor was located from 14-18 cm from the incisors. Laryngeal edema required emergency tracheostomy which was closed after 30 days. Although dysphagia decreased and this patient was classified as a partial response, it is unlikely that the patient received net benefit from PDT therapy.

Patient
Looks like the TEF occurred in course 2, though it is listed as occurring in course 1.

Course 2 day 8 removed because of suspicion of perf. Died d 25 esoph hemorrhage. Things seemed ok until (ps 90%, grade I dysphagia) that second treatment then rapidly deteriorated.

Guide wire passing/dilating/stent appeared to either go into or form fistula at one month or so.

Fistula with second course. No good details, seemed to be related to deterioration.

Fistula one month into course 2, about 5 months from first PDT RX.

TE fistula occurring about 15 days after PDT laser application. . Pt died 2-3 wks later.

This pt had early problems with sepsis and ARDS and a TE fistula later at 2 months. She lived nearly a year. I am not so sure the ARDS is not related.

This pt. had anemia as reason for going offstudy. Anemia drastically worsened on day 3, and was attributed to GI bleed. Investigator seemed to think it wasn't rx related, but I wonder about low esophageal bleed.

Pt. broke hip while reaching for flashlight in dark room.

This patient had possible TEF noted on day 7 and subsequently was intubated. He never got

V.

off ventilator and died on day 34.

Pt. had 3 days of stridor after rx of lesion at 18 cm. Bronchoscopy on d 31 noted TEF.

Tumor at 25 cm. TE fistula noted day 10. Died day 32 of infection attributed to TEF and hence PDT.

Appendix 3

Number of Grade III and IV AE's with PDT Before and After Lyophilized Formulation:

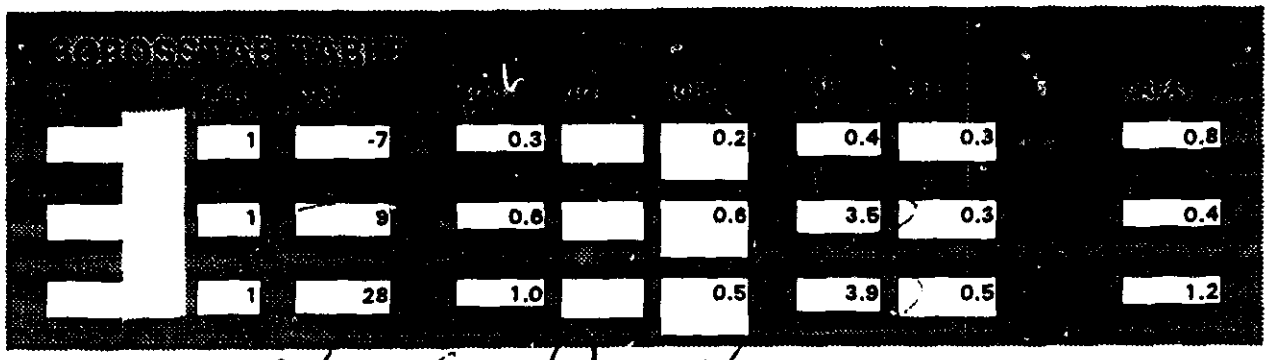
(Normalized to 100 Patients, according to patients randomized before or after 1/10/90)

CAT	AE	before	after	nBefore	nAfter	n(ratio)
AUTONOMIC NERVOUS SYSTEM	GLAUCOMA	1		2.4	0	0.0
AUTONOMIC NERVOUS SYSTEM	HYPERTENSION	2		4.9	0	0
AUTONOMIC NERVOUS SYSTEM	HYPOTENSION	2		4.9	0	0
AUTONOMIC NERVOUS SYSTEM	ILEUS	1		2.4	0	0
AUTONOMIC NERVOUS SYSTEM	SYNCOPE	1		2.4	0	0
BODY AS A WHOLE	ASCITES	2		4.9	0	0
BODY AS A WHOLE	ASTHENIA	3		7.3	0	0
BODY AS A WHOLE	BACK PAIN	2		4.9	0	0
BODY AS A WHOLE	CHEST PAIN	4	2	9.8	2.6	0.3
BODY AS A WHOLE	CHEST PAIN SUBSTERNAL	1	1	2.4	1.3	0.5
BODY AS A WHOLE	FATIGUE		1	0	1.3	#DIV/0!
BODY AS A WHOLE	FEVER	2	2	4.9	2.6	0.5
BODY AS A WHOLE	OEDEMA		1	0	1.3	#DIV/0!
BODY AS A WHOLE	OEDEMA GENERALIZED	2	1	4.9	1.3	0.3
BODY AS A WHOLE	PAIN	4	4	9.8	5.2	0.5
CARDIOVASCULAR	CARDIAC FAILURE	2	2	4.9	2.6	0.5
CENTRAL NERVOUS SYSTEM	CONVULSIONS	1		2.4	0	0
CENTRAL NERVOUS SYSTEM	HEADACHE	1		2.4	0	0
CENTRAL NERVOUS SYSTEM	HYPOKINESIA	1		2.4	0	0
CENTRAL NERVOUS SYSTEM	OPTIC NEURITIS	1		2.4	0	0
CENTRAL NERVOUS SYSTEM	PARALYSIS	1		2.4	0	0
GASTROINTESTINAL	ABDOMINAL PAIN	9	2	22	2.6	0.1
GASTROINTESTINAL	CONSTIPATION	3		7.3	0	0
GASTROINTESTINAL	DIARRHEA	1		2.4	0	0
GASTROINTESTINAL	DYSPEPSIA	1		2.4	0	0
GASTROINTESTINAL	DYSPHAGIA	2	2	4.9	2.6	0.5
GASTROINTESTINAL	ERUCTATION	1		2.4	0	0
GASTROINTESTINAL	GI HAEMORRHAGE	2	2	4.9	2.6	0.5
GASTROINTESTINAL	HAEMATEMESIS	3	4	7.3	5.2	0.7
GASTROINTESTINAL	HICCUP		1	0	1.3	#DIV/0!
GASTROINTESTINAL	INTESTINAL STENOSIS	1		2.4	0	0
GASTROINTESTINAL	MELAENA	1		2.4	0	0
GASTROINTESTINAL	OESOPHAGEAL STRICTURE	2	2	4.9	2.6	0.5
GASTROINTESTINAL	OESOPHAGEAL ULCERATION	3		7.3	0	0
GASTROINTESTINAL	OESOPHAGEAL ULCERATION HAEMORRHAG	3		7.3	0	0

GASTROINTESTINAL	OESOPHAGITIS		1	0	1.3	#DIV/0!
GASTROINTESTINAL	PERITONITIS		1	0	1.3	#DIV/0!
GASTROINTESTINAL	S T O M A T I T I S ULCERATIVE	1		2.4	0	0
GASTROINTESTINAL	VOMITING	4	2	9.8	2.6	0.3
HEART RATE/RHYTHM	CARDIAC ARREST	2		4.9	0	0
HEART RATE/RHYTHM	FIBRILLATION ATRIAL	3	1	7.3	1.3	0.2
HEART RATE/RHYTHM	TACHYCARDIA	2		4.9	0	0
LIVER AND BILIARY	CHOLECYSTITIS	3		7.3	0	0
LIVER AND BILIARY	JAUNDICE	2		4.9	0	0
METABOLIC & NUTRITIONAL	ACIDOSIS	1		2.4	0	0
METABOLIC & NUTRITIONAL	DEHYDRATION	1	1	2.4	1.3	0.5
METABOLIC & NUTRITIONAL	HYPERCALCAEMIA	1	1	2.4	1.3	0.5
METABOLIC & NUTRITIONAL	WEIGHT DECREASE	1		2.4	0	0
MUSCULO-SKELETAL	ARTHRALGIA		1	0	1.3	#DIV/0!
MUSCULO-SKELETAL	BONE DISORDER	1		2.4	0	0
MUSCULO-SKELETAL	F R A C T U R E PATHOLOGICAL	2		4.9	0	0
MYO-,ENDO-,PERICARDIAL & VALVE	ANGINA PECTORIS	1		2.4	0	0
MYO-,ENDO-,PERICARDIAL & VALVE	ENDOCARDITIS		1	0	1.3	#DIV/0!
MYO-,ENDO-,PERICARDIAL & VALVE	M Y O C A R D I A L INFARCTION	2		4.9	0	0
PSYCHIATRIC	AGITATION	1		2.4	0	0
PSYCHIATRIC	AMNESIA	1		2.4	0	0
PSYCHIATRIC	ANOREXIA	4		9.8	0	0
PSYCHIATRIC	CONFUSION	2		4.9	0	0
PSYCHIATRIC	INSOMNIA		1	0	1.3	#DIV/0!
RED BLOOD CELL	ANAEMIA	11	1	26.8	1.3	0
RESISTANCE MECHANISM	INFECTION		1	0	1.3	#DIV/0!
RESISTANCE MECHANISM	SEPSIS	2	3	4.9	3.9	0.8
RESPIRATORY	APNOEA	1		2.4	0	0
RESPIRATORY	ASPIRATION	1		2.4	0	0
RESPIRATORY	BRONCHOSPASM	1		2.4	0	0
RESPIRATORY	CHEST X-RAY ABNORMAL		1	0	1.3	#DIV/0!
RESPIRATORY	COUGHING	1		2.4	0	0
RESPIRATORY	DYSPNOEA	5	1	12.2	1.3	0.1
RESPIRATORY	HAEMOPTYSIS	1		2.4	0	0
RESPIRATORY	PHARYNGITIS	1	1	2.4	1.3	0.5
RESPIRATORY	PLEURAL EFFUSION	4	3	9.8	3.9	0.4
RESPIRATORY	PLEURISY		1	0	1.3	#DIV/0!
RESPIRATORY	PNEUMONIA	7	7	17.1	9.1	0.5
RESPIRATORY	P U L M O N A R Y HAEMORRHAGE	1		2.4	0	0
RESPIRATORY	P U L M O N A R Y INFILTRATION	1		2.4	0	0

RESPIRATORY	PULMONARY OEDEMA	1		2.4	0	0
RESPIRATORY	RESPIRATORY INSUFFICIENCY	8	6	19.5	7.8	0.4
RESPIRATORY	STRIDOR		1	0	1.3	#DIV/0!
RESPIRATORY	TRACHEO-OESOPHAGEAL FISTULA	7	11	17.1	14.3	0.8
SKIN AND APPENDAGES	CELLULITIS		1	0	1.3	#DIV/0!
URINARY	HYDRONEPHROSIS	1		2.4	0	0
URINARY	RENAL FAILURE ACUTE		1	0	1.3	#DIV/0!
URINARY	RENAL FUNCTION ABNORMAL	2		4.9	0	0
URINARY	URINARY TRACT INFECTION	1	1	2.4	1.3	0.5
VASCULAR (EXTRACARDIAC)	CEREBROVASCULAR DISORDER	4	2	9.8	2.6	0.3
VASCULAR (EXTRACARDIAC)	PERIPHERAL ISCHAEMIA	1		2.4	0	0
VASCULAR (EXTRACARDIAC)	THROMBOPHLEBITIS	1		2.4	0	0
VISION	EYE PAIN	1		2.4	0	0
VISION	VISION ABNORMAL	2		4.9	0	0

Appendix 4

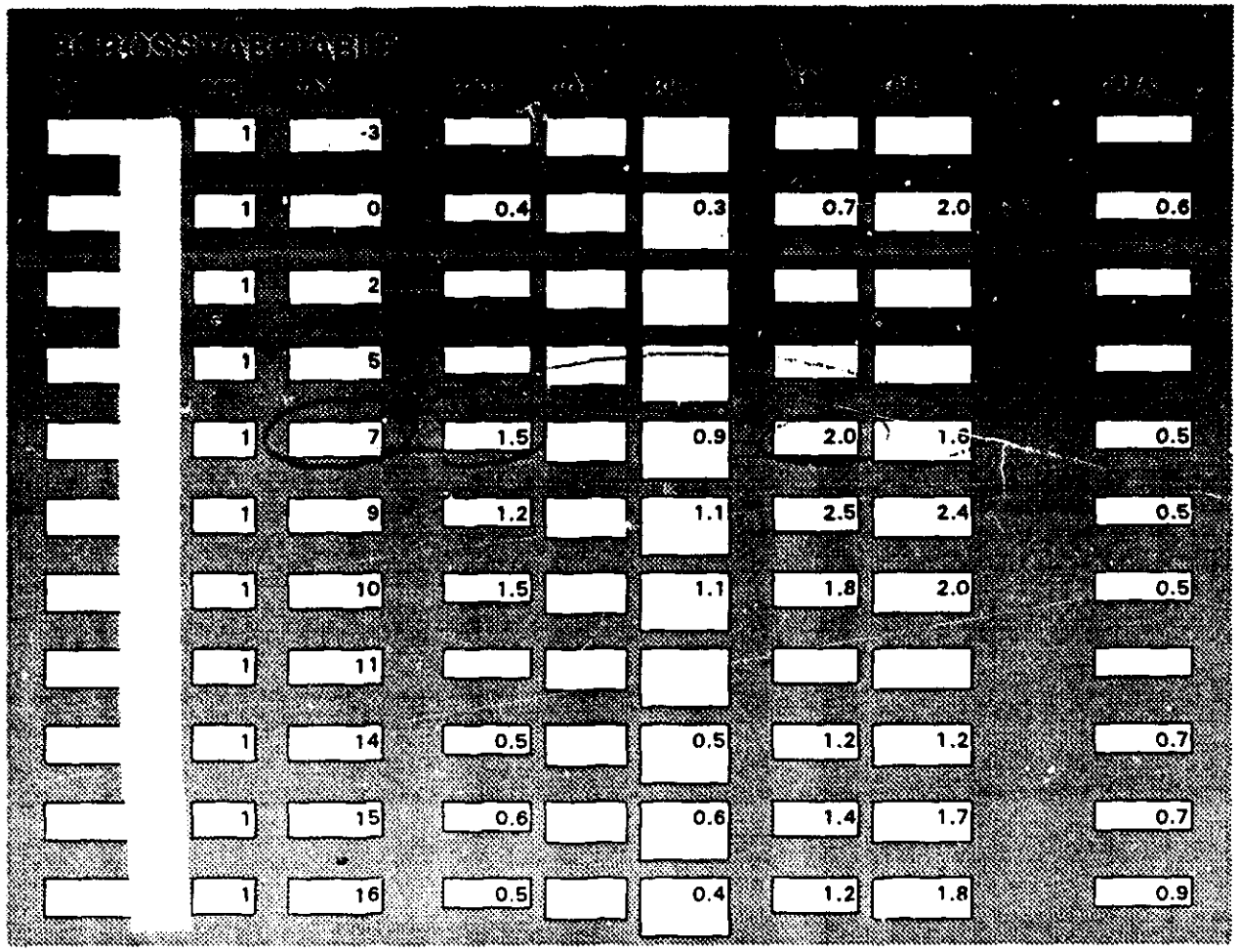


	1	-7	0.3		0.2	0.4	0.3	0.8
	1	9	0.6		0.6	3.5	0.3	0.4
	1	28	1.0		0.5	3.9	0.5	1.2

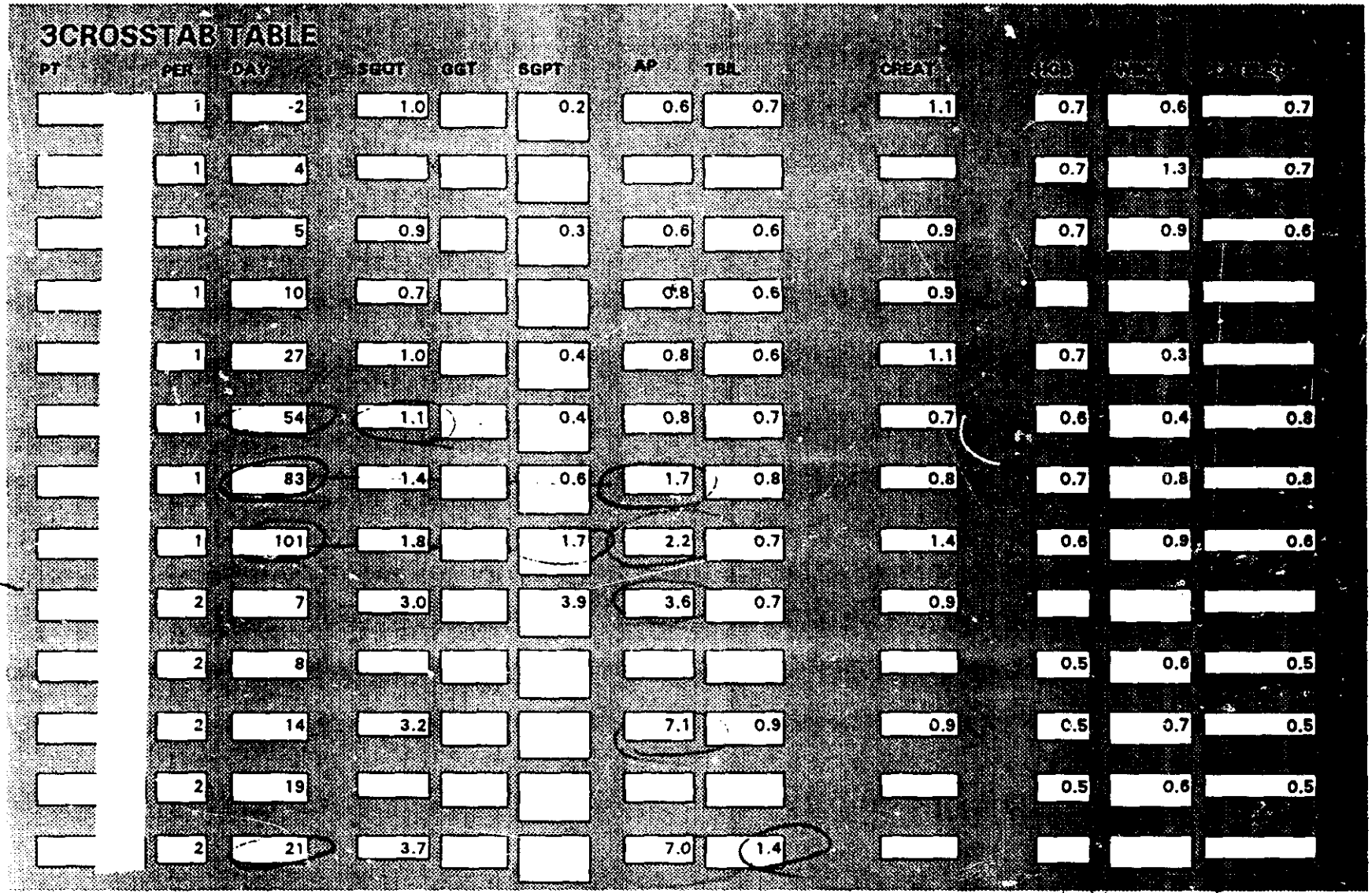
Clarify P...

X

Appendix

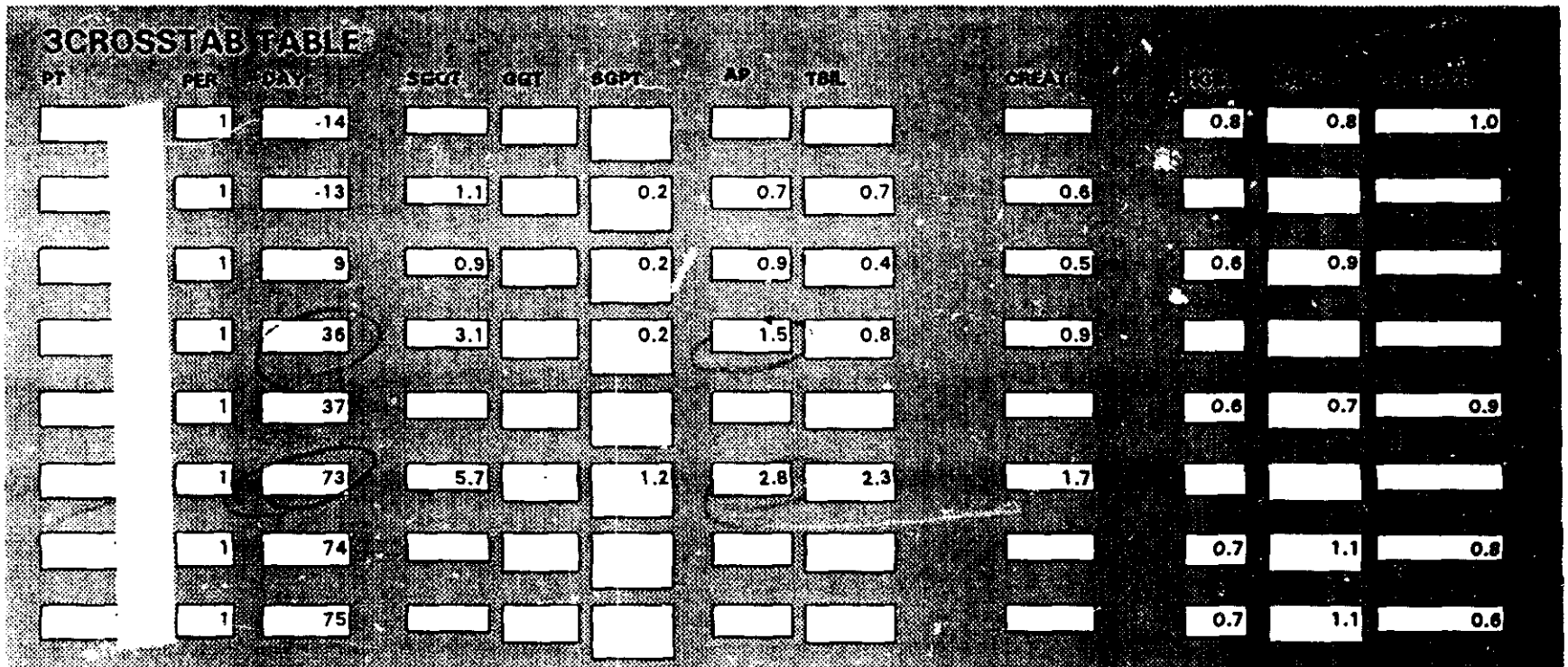


1	-3						
1	0	0.4		0.3	0.7	2.0	0.6
1	2						
1	5						
1	7	1.5		0.9	2.0	1.6	0.5
1	9	1.2		1.1	2.5	2.4	0.5
1	10	1.5		1.1	1.8	2.0	0.5
1	11						
1	14	0.5		0.5	1.2	1.2	0.7
1	15	0.6		0.6	1.4	1.7	0.7
1	16	0.5		0.4	1.2	1.8	0.9



3CROSSTAB TABLE

PT	PER	DAY	SGOT	GGT	SGPT	AP	TBIL	CREAT			
	1	-2	1.0		0.2	0.6	0.7	1.1	0.7	0.6	0.7
	1	4							0.7	1.3	0.7
	1	5	0.9		0.3	0.6	0.6	0.9	0.7	0.9	0.6
	1	10	0.7			0.8	0.6	0.9			
	1	27	1.0		0.4	0.8	0.6	1.1	0.7	0.3	
	1	54	1.1		0.4	0.8	0.7	0.7	0.6	0.4	0.8
	1	83	1.4		0.6	1.7	0.8	0.8	0.7	0.8	0.8
	1	101	1.8		1.7	2.2	0.7	1.4	0.6	0.9	0.6
	2	7	3.0		3.9	3.6	0.7	0.9			
	2	8							0.5	0.6	0.5
	2	14	3.2			7.1	0.9	0.9	0.5	0.7	0.5
	2	19							0.5	0.6	0.5
	2	21	3.7			7.0	1.4				

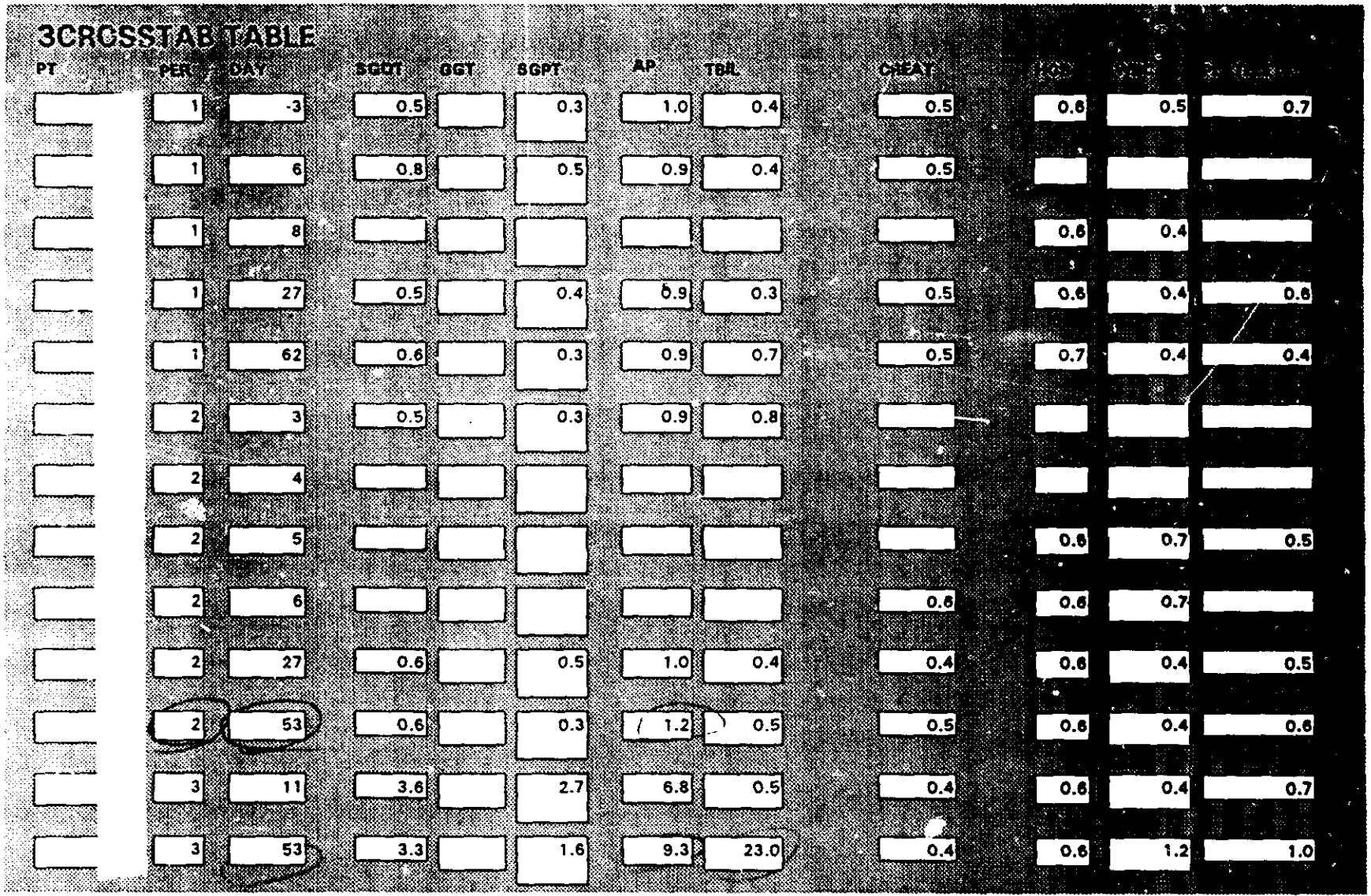


3CROSSTAB TABLE

PT	PER	DAY	SGOT	GGT	SGPT	AP	TBIL	CREAT	K		
	1	-14							0.8	0.8	1.0
	1	-13	1.1		0.2	0.7	0.7	0.6			
	1	9	0.9		0.2	0.9	0.4	0.5	0.6	0.9	
	1	36	3.1		0.2	1.5	0.8	0.9			
	1	37							0.6	0.7	0.9
	1	73	5.7		1.2	2.8	2.3	1.7			
	1	74							0.7	1.1	0.8
	1	75							0.7	1.1	0.6

Doc Pt in CRF Manual
Taxotere for Lung NOS —
Poorly Documented on CRF

XIII



3CRCSSTAB TABLE

PT	PER	DAY	SGOT	GGT	SGPT	AP	TBIL	CREAT			
	1	-3	0.5		0.3	1.0	0.4	0.5	0.6	0.5	0.7
	1	6	0.8		0.5	0.9	0.4	0.5			
	1	8							0.6	0.4	
	1	27	0.5		0.4	0.9	0.3	0.5	0.6	0.4	0.6
	1	62	0.6		0.3	0.9	0.7	0.5	0.7	0.4	0.4
	2	3	0.5		0.3	0.9	0.8				
	2	4									
	2	5							0.6	0.7	0.5
	2	6						0.6	0.6	0.7	
	2	27	0.6		0.5	1.0	0.4	0.4	0.6	0.4	0.5
	2	53	0.6		0.3	1.2	0.5	0.5	0.6	0.4	0.6
	3	11	3.6		2.7	6.8	0.5	0.4	0.6	0.4	0.7
	3	53	3.3		1.6	9.3	23.0	0.4	0.6	1.2	1.0

28

3CROSSTAB TABLE

PT	PER	DAY	SGOT	GGT	SGPT	AP	TBIL	CREAT	HGB	WBC	PLATELETS
	1	-3	0.8		0.3	0.7	0.4	0.6	0.7	0.7	0.4
	1	9	0.9		0.7	1.3	0.3	0.5	0.6	1.0	0.7
	1	29	1.2			2.7	0.3	0.4			
	1	32							0.8	1.4	
	1	46							0.6	1.1	0.5
	1	51	1.2			3.8	0.7	0.5			
	1	56							0.5	1.0	0.7
	1	58							0.5	1.3	0.7
	1	59							0.7	1.4	0.8
	1	62							0.7	0.8	0.4
	1	64									
	1	65	1.1		0.5	1.4	6.1	0.5	0.8		
	1	71							0.6	1.0	0.5
	1	72							0.7	1.3	0.8
	1	75	3.4		2.6	5.1	5.9	0.7			

Abd effusion Tapped — not doing well [illegible] — [illegible] — TCA [illegible] well explained.

XV

24:1971

3CROSSTAB TABLE

P/	PER	DAY	SGOT	GGT	SGPT	AP	TBIL	CREAT	HGB	[illegible]	[illegible]
	1	-30						0.7			
	1	-4	1.3			0.9	0.4		0.7	0.7	0.8
	1	9	1.1			0.9	0.6	0.5	0.7	0.9	0.7
	1	31							0.7	1.4	0.8
	1	36	4.9			2.7	1.0	0.8			
	2	7	24.3			5.0			0.8	2.7	1.0
	2	8						2.2			

OK D9

D 36: AP 2.7 GOT 4.7

Fever Day 12 — Effusions — At Ticar Cont

Hepatic Mg — Echemia → (? 2° to Drug Dz)

XVI

8:GT/

XVII

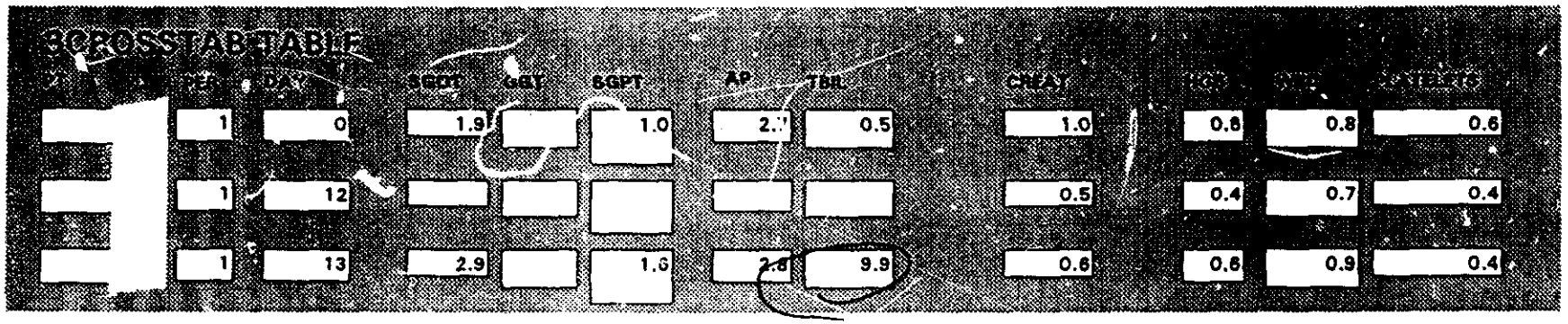
3CROSSTAB TABLE

[illegible]	PER	DAY	SGOT	GGT	SGPT	AP	TBIL	CREAT	K	[illegible]	[illegible]
	1	-19	0.3		0.1	1.6	0.3	0.6	0.6	1.6	1.2
	1	0	5.0		3.3	4.9	0.5	0.5	0.6	1.4	1.2
	1	9	2.6		2.1	10.0	9.5	0.5			
	1	16							0.6	1.7	1.5
	1	34	0.3		0.2	2.1	0.9	0.5	0.6	1.6	1.1
	1	64	0.4		0.2	2.1	0.5	0.4	0.6	1.7	1.3
	2	8							0.5	1.2	1.0
	2	10	1.3		1.?	6.0	1.0	0.5	0.6	1.9	1.2

6/i> Sx wt

– ERCP STENT – Day 14 –

Tumor Related



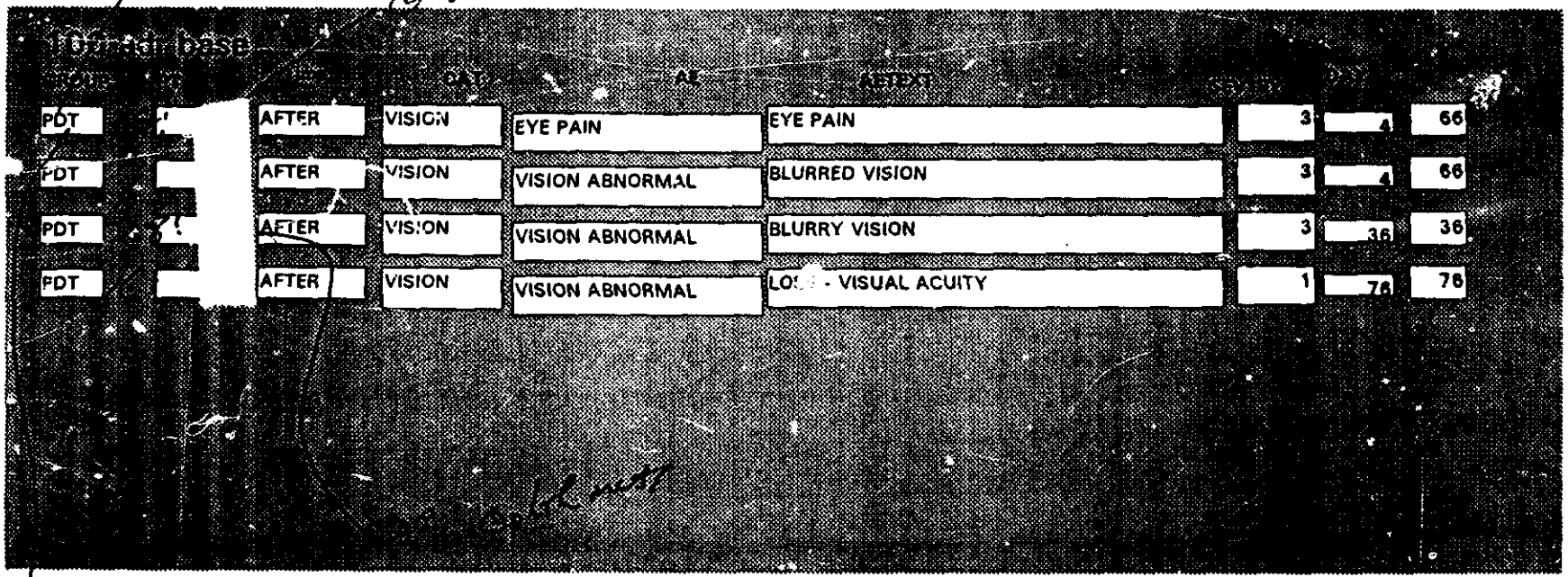
Liver Mets

XVIII

136 156

Glaucoma & Acute Loss of Vision ★

XIX



PDT		AFTER	VISION	EYE PAIN	EYE PAIN	3	4	66
PDT		AFTER	VISION	VISION ABNORMAL	BLURRED VISION	3	4	66
PDT		AFTER	VISION	VISION ABNORMAL	BLURRY VISION	3	36	36
PDT		AFTER	VISION	VISION ABNORMAL	LOS[illegible] - VISUAL ACUITY	1	76	76

Acute Loss of Vision for Laser Rx

Appendix - 5

Note 2/19 Acute visit Blurred Vision

Rt 2/13/91

P. Zimmerman

SEP 13 1994

Medical Officer Review #2 (Photofrin)

1.0 General Information:

1.1 NDA# 20-451
1.1.2 Review: M.O. Review #2
1.1.3 Submission date: April 14, 1994
1.1.4 Date of Review September 6, 1994

1.2 Drug Name
1.2.1 Generic name: Sterile porfimer sodium
1.2.2 Trade name: Photofrin

1.3 Applicant: Quadralogic Technologies Inc.

1.4 Pharmacologic Category: Photosensitizer, antineoplastic agent

1.5 Proposed indication: Complete or partially obstructing esophageal cancer.

TABLE OF CONTENTS

(continued next page)

Introductory Comments

Medical Officer Review #1 concentrated on the efficacy and safety data of the largest study (P19 in partially obstructing esophageal cancer) as it was reported in the Applicant's Final Study Report and as analyzed by the reviewer from the electronic data submitted by the applicant. In addition to reviewing the 17-patient study of patients with completely obstructing esophageal cancer (p20) this review will cover the Applicant's integrated summaries of safety and efficacy. The following points from the reviewer introduction to section 7 of this review are pertinent to consider here:

> "The integrated summary of efficacy located in volume 42 of the NDA is the subject of this section of Medical Officer Review #2. In addition to overview analyses and tables of analyses done in the individual studies, the sponsor also presents some new ways of viewing data on primary patients.
>
> In this section of MOR#2 the FDA reviewer wishes to accomplish several purposes:
> - to document several of the applicant's summary tables for reference.
> - to discuss new analyses of the efficacy data presented by the sponsor.
> - to present the applicant's summary and conclusions.
>
> Much of this section will represent verbatim tables and text prepared by the applicant in the 150-page efficacy summary. Interspersed will be reviewer comments and conclusions. Special attention should be given to the sponsor's presentation of *"Patients with a Clinically Important Benefit from PDT."* This presents a graphical attempt to portray risk and benefit of selected patients and was not part of the P19 study report."

The integrated summary of safety also contained some new perspectives on the clinical significance of side effects in the P19 and P20 studies.

Manufacturing issue:

An important issue which is still under review is the issue of a manufacturing change that occurred toward the end of the P19 study. This is a completely different issue from the formulation (frozen vs lyophilized) issue discussed in MOR #1 and MOR #2. The manufacturing issue will be discussed in depth in a later medical officer review after the Applicant has performed its own analyses. It will not be discussed in depth with the advisory committee at this time. Introductory comments on this topic from MOR#3 follow:

> "In addition to the change in formulation over the life of the P19 study, there were changes in manufacturing process. The 3 processes are labeled The drug substance for this NDA uses process The biggest change in process occurred with the change to This change led to a larger proportion of as opposed to in the drug substance. See Chemistry Review for details on these changes. Only 27 patients in the P19

study received drug prepared by scheme II."

The following will be important questions for the sponsor to consider regarding the manufacturing change:

- Given the chemical changes in drug product, how ciinically significant might we expect the changes to be?
- What evidence do we have that efficacy and safety are not significantly different after the manufacturing change?
- Is the difference in toxicity profile noted concurrent with change to lyophilized formulation actually due to the concurrent manufacturing change to scheme II?

3.0 Material Reviewed/Clinical Data Source

The following is the location of documents in the NDA as listed in Medical Review #1.

As noted in bold below the study report for study P-20, the main topic of this Medical Review #2, is located in volumes 40-41.

NDA 20-451: 164 volumes

Key Volume Numbers:

TOPIC	VOLUME
Labeling	1
Pharmtox	9
PK	28
Clinical	30-54
Study 73-19	33
Protocol	34
Patient Profiles	36-37
Listings	38-39
CRF Tabulations	100-102
CRFs	107-164
Study 73-20	**40-41**
Other studies	42
Summary of Efficacy	**43**
Summary of Safety	**44**
Integrated Summary	54
Literature	55-77

6.1 Trial P20

6.1.1 Protocol Review

Study P20:

Title: A PHASE III STUDY OF SAFETY AND EFFICACY OF PDT UTILIZING PHOTOFRIN II IN PATIENTS WITH COMPLETELY OBSTRUCTING ESOPHAGEAL CARCINOMA.

Review of Original Protocol

This study was a open-label single arm study of PDT in patients with completely obstructing esophageal cancer. A minimum of 25 patients were to be recruited over 18 months.

Entry criteria:

Major entry criteria are listed below:

- biopsy proven Stage T1-T3, any N, any M, too debilitated or refused chemotherapy or surgery or failed to respond or recurred after Rx.
- Completely obstructing esophageal cancer (cannot pass guidewire)
- KPS >= 30
- Excluded for tracheal or carinal involvement with tumor

Procedure:

Photofrin was given by slow IV push over 3-5 min. at 2 mg/kg. Laser light at 630 nm was applied at 40-50 hours with a second light treatment allowed at 96 to 120 hrs. Microlens diffusing fibers were used for tumors less than or equal to 0.5cm in diameter using light at a power density of 200mW/cm2 for a total of 100 j/cm2. For larger lesions cylindrical diffusing fiber tips were used at 400 mW/cm of fiber tip for a total power of 300 J/cm.. Diffusing fibers were inserted into the center of the mass until completely inserted or until significant resistance was encountered. Up to 3 Photofrin injections were allowed at a minimum time-interval of 30 days. Endoscopy for debridement of necrotic tumor was to occur 2 days after each laser treatment. .

Efficacy

Efficacy was to be evaluated at each treatment session, at end of treatment, monthly X 3 and at 6 mo.

Primary Endpoints:

- Objective tumor response
- Symptom palliation (dysphagia grade and duration)

Secondary Endpoints

- Change in Karnofsky performance status
- Weight change
- Time to treatment failure.
- Survival

Tumor response was to be confirmed in a blinded fashion by a panel using esophagograms and videotapes. Any change in dysphagia grade was to be the primary endpoint for symptom palliation.

Time to treatment failure was defined as time to removal from study for any of the following:

- Disease progression
- Unacceptable Toxicity
- Death
- Any treatment related reason(patient request, investigator request)

Response Criteria (As amended August, 1988 before any patients were entered on Protocol):

Partial response:	-50% decrease in length and cross-sectional diameter of tumor or appearance of visible lumen.
Progressive disease:	-Increase in any tumor margin, marked decrease in diameter of lumen ,or reappearance of tumor
Complete response:	-Absence of Tumor by endoscopy

Followup

Studies to be done at baseline, 1wk, 1mo, 2mo, 3mo, 6 mo included the following:

- CT of Liver and esophagus
- Endoscopy
- Labs and CXR at baseline,.
- Esophagogram
- KPS
- Dysphagia Grade (same scale as that used in study P19)

Patients were to be removed from study for no evidence of palliation or response after 2 courses of PDT or unacceptable toxicity.

Protocol Amendment:

In October 1989 the protocol was amended to include use of the new lyophilized formulation.

6.1.2 Study implementation:

Endpoints as Analyzed:

Changes were made to the original Protocol plan; time to treatment failure was expanded to include worsening dysphagia. The definition of response deleted tumor length and cross-sectional area. As analyzed, response was based solely on new appearance of a lumen and change in lumenal diameter. Data conventions are similar as those in P20 (for instance Week1 = day 1-17 and month 1 = day 18-day 45).

The following are the time dependent efficacy endpoints as actually analyzed in the trial:

Time to treatment failure

- Objective disease progression within esophageal lumen
- Worsening of dysphagia due to tumor
- Dilatation at 1 month or beyond for any reason
- Retreatment
- Termination due to treatment-related toxicities or complications
- Death
- Patient or investigator request for withdrawal
- Disease progression outside esophageal lumen and/or overall patient deterioration,
- Therapeutic failure (failure to achieve a CR or PR)
- Protocol violation (Restricted to violations that resulted in a significant deviation from protocol specified delivery of therapy.

Time to palliation failure

- Worsening dysphagia
- Failure to palliate
- Termination due to treatment-related toxicity or treatment-related death
- Dilatation
- Retreatment

Reviewer comments:

The Applicants states that these endpoints were formulated, or redefined, after study completion but before analysis of the data. As in study P19, these endpoints are somewhat vague and difficult to define in an individual patient. However, even if better defined, these time-dependent endpoints could not really be seriously evaluated in a small non-comparative study such as this.

6.1.3 Eligibility and Demographics

Accrual:

19 patients were enrolled from April 13, 1989 to August 25, 1992.

32 centers were enlisted. 8 centers enrolled at least one patient:

Investigator, location	# Pts.
Lightdale, NyNY	5
Jacobs , Kansas City	2
Stiegmann,k U of Colorado	3
Mirhoseini, Milwaukee, WI	2
Schweitzer, Detroit, MI	2
Aronchick, Philadelphia, PA	2
Locicero, Boston, MA	2
Pietrafitta, Boston, MA	1

At baseline 5 pts had luminal openings at the proximal margin of tumor (Pt and 2 of these were ineligible since lumen extended through tumor (Pt.). 2 patients were never treated because of a non-functioning laser in one case and because of rapid clinical deterioration from brain metastases in the other case. So, 15 eligible pts. were treated. 8 patients went on to receive a second course of PDT.

Above data are summarized in Applicant's table 10 A:

Table 10A. Summary of Patient Eligibility at First Course

	PDT	
	No.	(%)
No. Enrolled	19	(100)
No. Eligible	17	(89.5)
No. Ineligible	2	(10.5)
Reason Ineligible		
Measurable Lumen at Baseline	2*	

* One of these ineligible patients (Pt. No. , was removed from study prior to treatment at the request of his wife due to deterioration of pt.'s condition as a result of brain metastasis.

Completeness of data collection is summarized in the Applicant's table 10C:

Table 10C. Summary of Reasons Dysphagia Grades Were Not Available for First Course By Visit for All Enrolled Patients

	Week 1 No.	(%)	Month 1 No.	(%)
Enrolled	19	(100)	19	(100)
No. Treated	17		17	
No. with Available Data	17	(89.5)	10	(52.6)
No. with No Available Data	2	(10.5)	9	(47.4)
Reasons Data Not Available				
On Study	0		1	
No Evaluation Performed			1	
Off Study	2		8	
Death	0		2	
Other than Death	2			

Completeness of data for objective response was very similar (Sponsor's table 10D, not reproduced for this review).

The sponsor states:

> "Evaluability was assessed for only the Week 1 and Month 1 visits of Course 1, since these were the primary timepoints for the efficacy analyses."

The choice of time of primary analysis was made at time of analysis since it was not specified in the protocol.

Treatment received

The number of laser applications during each course is summarized in table 10G from the Applicant's application:

Table 10G.
Distribution of Laser Applications Per Course of Treatment
for All Treated Patients

	PDT	
	No.	(%)
No. Enrolled	19	
No. Treated	17	(100)
No. Pts. Receiving First Course*	17	(100)
No. Laser Applications		
1	4	
2	12	
3**	1	
No. Pts. at Second Course***	8	(47.1)
No. Laser Applications		
1	5	
2	3	
No. Pts. at Third Course***	1	(5.9)
No. Laser Applications		
1	1	

* One course of PDT is one injection of PHOTOFRIN® and up to 2 laser light applications.

** Patient No. receiving 3 laser applications which is a violation of the protocol.

*** A total of 3 treatment courses were allowed. Treatment courses had to be separated by at least 30 days between injections.

Debridement was to be performed 2-4 days after first laser Rx. The sponsor's table 10G summarizes compliance with debridement

Table
10H.
Compliance with Protocol Specified Debridement After
First Laser Application Of First Course

	PDT	
	No.	(%)
No. Enrolled	19	
No. Treated	17	(100)
Compliance	8	(47.1)
Non-Compliance	9	(52.9)
Debridement Not Done	4	
Debridement Performed Outside Specified Time Interval	5	

13/17 of the patients received the newer lyophilized formulation.

The number of endoscopies required for the first course of treatment is summarized in the Sponsor's table 11d:

Table 11D. Distribution of Treatment Procedures by Number of Endoscopies for All Treated Patients at First Course

	Number of Endoscopies									
	1		2		3		4		Total	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
No. Treated	1	(5.9)	6	(35.3)	8	(47.1)	2	(11.8)	17	(100)
Total Endoscopies	1		12		24		8		45	
Laser Only	1		8		10		4		23	
Debridement Only	0		3		5		3		11	
Combination*	0		1		7		0		8	
Assessment Only**	0		0		2		1		3	

* Combination = endoscopy during which **both** laser application and debridement were performed.
** Assessments were endoscopies intended for debridement but no debridement was necessary.

About half the sessions involved laser and about half involved debridement; some sessions involved both laser application and debridement. 3/4 of the patients completed therapy within 10 days.

Patient Disposition

The sponsor's table 10I summarizes patient disposition.. All patients are offstudy. 6 died onstudy, 1 progressed, and the rest went offstudy for a variety of reasons:

Table 10I. Disposition of All Patients

	PDT No.	(%)
No. Enrolled	19	(100)
Study Status		
On-Study	0	(0)
Off-Study	19	(100)
Death	6	
Disease Progression	1	
Patient Request Withdrawal	2	
Fail to Achieve CR/PR	1	
Other	9	
Fistula Formation	2*	
Patient Very ill	1	
Patient Deterioration	2**	
Laser Problems	1	
Therapy Changed	2	
Completed Protocol	1	
Survival Status		
Deceased	18	(94.7)
Unknown/Lost-to follow-up	1	(5.2)

* Patient No. had disease progression listed as off-study reason, but was terminated for fistula formation.

** Patient No. had disease progression listed as off-study reason, but was terminated due to deterioration of condition secondary to brain metastasis.

Baseline characteristics:

Baseline characteristics are summarized in the sponsor's table 10J:

Table 10J. Patient Pretreatment Characteristics for All Patients

	PDT No.	(%)
No. Enrolled	19	(100)
Sex		
Male	10	(52.6)
Female	9	(47.4)
Age (years)		
<60	3	(15.8)
≥60	16	(84.2)
Median	68	
(Range)	(41 - 86)	
Race		
Caucasian	15	(78.9)
Black	4	(21.1)
Karnofsky Performance Status (%)		
81-100	6	(31.6)
61-80	7	(36.8)
41-60	4	(21.1)
31-40	2	(10.5)
Median	70	
(Range)	(40 - 90)	
Dysphagia Grade		
4	7	(36.8)
5	12	(63.2)
Weight (kg)		
30-39	1	(5.3)
40-49	4	(21.1)
50-59	5	(26.3)
60-69	5	(26.3)
≥ 70	4	(21.1)
Median	56	
(Range)	(34 - 98)	

7 patients had a dysphagia grade of 4 (Difficulty in swallowing liquids) and 12 had grade 5 (unable to swallow saliva). Median age was 68 years.

Prior therapy is summarized in the sponsor's table 10K:

Table 10K. Prior Disease History, Prior Therapy Usage and Extent of Disease Involvement at Baseline for All Patients

	PDT No.	(%)
No. Enrolled	19	(100)
Disease Presentation at Enrollment		
Esophageal Carcinoma	18	(94.7)
Gastroesophageal Junction	1	(5.2)
Prior Therapy Usage		
No Prior Therapy	7	(36.8)
Stage I	1	
Stage II	1	
Stage III	5	
Prior Therapy	12	(63.2)
M0	8	
M1	4	
Interval from Diagnosis to Enrollment (mos)		
≤ 6	9	
> 6 - 12	1	
>12 - 24	7	
> 24	2	
Median (Range)	9	

12 of the 19 patients had prior therapy, (chemotherapy, radiation therapy, surgery, and/or Nd:YAG).

Baseline tumor characterisitics are shown in the sponsor's table 10M:

Table 10M. Baseline Histology and Tumor Size and Location for All Patients

	PDT No.	(%)
No. Enrolled	19	(100)
Histology		
Squamous Cell	9	(47.4)
Adenocarcinoma*	10	(52.6)
Location in Esophagus**		
Upper 1/3	9	(47.4)
Middle 13	6	(31.6)
Lower 1/3	4	(21.1)
Tumor Length (cm)***		
< 10 cm tumor	5	(26.3)
1-5	2	
6-9	3	
≥ 10 cm tumor	4	(21.1)
Unknown	10	(52.6)

* One patient had disease at the GE junction.
** Tumor location was based on the proximal tumor margin.
*** Tumor length was based on both proximal and distal tumor margins.

Most tumors were in the upper 2/3 of the esophagus and were less than 10 cm in length.

6.1.4 Efficacy analyses

6.1.4.1 Dysphagia analyses

Dysphagia data for the 19 patients is displayed individually in table 12A from the application (attached).

Reviewer comments.

I have made bold the 7/15 eligible (ie completely obstructed) patients who have an improvement in dysphagia grade at one month. As the sponsor indicates, one of these had a perforation.

As shown, 5 patients had a dysphagia grade improvement at both 1 week and one month. 2 others with improvement at one month had complications (perforation and stricture). Of the 5 responders that had Grade 5 dysphagia at baseline, 3 improved one grade and one each improved 2 grades and 3 grades. Of the 12 patients with Grade 5 dysphagia at baseline, 5 responded both at one week and at one month. 6/19 patients showed no evidence of improvement at either 1 week or one month.

Table 12A. Dysphagia Grade at Baseline, One Week and One Month for All Patients at First Course

Pt. No.	Baseline	One Week	One Month
	5	**1**	**4**
	5	**2**	**4**
	5	**2**	**4**
	5	**4**	**2**
	5	**4**	**3**
	5	**5***	**1***
	4	**2**	**2**
	4	**3****	**3****
	4	**3**	**4**
	4	**4**	**4**
	5	*2*	*ND*
	4	3	ND
	5	3	OS
	5	5	OS
	5	5	OS
	4	2***	ND
	4	4	OS
	5	OS	OS
	5	*OS*	*OS*

OS = Off-study
ND = Not done
* Dysphagia grade assessment rendered not evaluable; patient had esophageal perforation.
** Dysphagia grade assessment rendered not evaluable; patient had esophageal stricture.
*** Dysphagia grade assessment rendered not evaluable; patient received more than two laser sessions (three sessions).

As shown in table 12B, of those with measurements at one week or one month, the average change from baseline grade was -1.4 and -1.5 respectively, but only half of the patients had a one-month measurement:

Table 12B. Change from Baseline in Dysphagia Grade Over Time at First Course

Visit	PDT No. Pts.*	PDT Avg. Score
Baseline	19	4.6
Week 1	17	3.2
(Avg. Change from Baseline)		(-1.41)
95% C.I. for Change		[-2.02, -0.80]
Month 1	10	3.1
(Avg. Change from Baseline)		(-1.50)
95% C.I. for Change		[-2.29, -0.71]
Month 2	3	3.7
(Avg. Change)		(-1.00)
Month 3	too few patients (1)	

Negative change indicates improvement from previous visit, positive change indicates worsening.

C.I. = Confidence Interval.

* Patients with available visit dysphagia scores.

The sponsor's table 12D summarized Time to Treatment Failure data:

Table 12D.
Summary of Time to Treatment Failure at First Course
for All Patients

	PDT	
	No.	(%)
No. Enrolled*	19	(100)
No. Failures	17	(89.5)
Worsening dysphagia	6	
With objective progression	3	
Without objective progression	3	
Dilatation	1	
Retreatment	3	
Treatment-related termination	2	
Death	2	
Inadequate Palliation	1	
Patient Deterioration	2	
No. Censored	2	(10.5)
Non-Treatment Related Termination+	2	
Median TTF (days)++	30	
Range		
95% C.I.+++	[19, 33]	

* For the 2 not treated patients, the enrollment date is used as the beginning of their interval.
\+ Includes laser failure and protocol violation in terms of treatment delivery.
++ Interpolated estimate.
+++ C.I. = Confidence Interval

Median TTF was 30 days. Similarly median 'Time to palliation failure' was 30 days. 3 patients were retreated.

6.1.4.2 Objective Response

Data on objective response is outlined in the sponsor's table 12G. 8 of the patients had a lumen visible at 1 month, though 3 of these had progressed compared to the one week assessment. The sponsor finds a response rate of 63% (12/19) at 1 week and 32% (6/19) at 1 month.

Table 12G. Smallest Luminal Diameter and Response Determinations at Baseline, One Week and One Month at First Course for All Enrolled Patients

Pt. No.	Baseline SLD* (cm)	One Week SLD* (cm)	One Week Response**	One Month SLD* (cm)	One Month Response**
	0.0	0.6	PR	not done	missing***
	0.0	not done	missing***	not done	missing***
	0.0	not done	missing	0.4	PR
	0.0	1.0	PR	1.0	PR
	0.2	0.8	PR	not done	missing
	0.0	1.2	PR	0.3	PD
	0.0	0.0	SD**	not done	missing***
	0.0	no tumor seen	CR3***	not done	missing
	0.3	0.7	PR[1]	not done	missing
	0.0	0.8	PR	1.0	PR
	0.9	not done	missing***	not done	missing***
	0.0	0.5	PR	not done	missing***
	0.0	0.8	PR	0.5	PR
	0.0	0.8	PR	0.2	PD
	0.3	0.3	SD	0.5	PR
	0.0	0.5	PR	1.5	PR
	0.0	1.0	PR	0.5	PD
	0.0	0.5	CR3	not done	missing
	0.0	0.5	PR	not done	missing***

* SLD = Smallest Luminal Diameter
** ACCO Response
*** Patient previously off-study
* Patient never treated
** Patient not evaluable due to invalid baseline measurement
*** Patient not evaluable due to protocol violation
1 Patient not evaluable due to pre-existing esophageal stricture

Reviewer comments:

The sponsor's data on efficacy from separate tables is combined in the following analysis. Patients with either a dysphagia response at one month (any improvement from baseline) or a lumenal response at one month (newly visible lumen at endoscopy) defined by comparison of baseline findings to findings at one month, without regard to findings at 1 week, are listed below:

The following list is a list of patients with response as defined by a dysphagia grade decrease at one month and/or a visible lumen at one month:

Patient #	1 mo dysphagia Response	1 mo objective Response
	R	R
	R	R
	R	R
	R	NR
	R	R
	NR	R
	R	R
	NR	R
	R	R
	R	R

From this one notes that all but one responder noted by dysphagia grade had a visible lumen at one month. Thus the subjective findings seem to be corroborated by the physical findings in most cases.

Further Courses of Therapy

8 of 19 received a second course of PDT. 7 of 8 of these were patients who responded at either 1 week or one month.

Dysphagia grades, including retreatment, are listed in the Sponsor's table 12J:

Table 12J. Dysphagia Grade at Baseline, One Week and One Month for Retreated Patients at Second Course

	First Course			Second Course		
Pt. No.	Baseline	One Week	One Month	Baseline	One Week	One Month
	5	1	4	4	1	ND
	5	2	ND	2	2	2
	5	2	4	4	3	4
	5	4	3	3	ND	OS
	4	2	2	2	3	OS
	4	3*	3*	3	ND	3*
	4	3	4	2	3	4
	4	4	4	4	4	OS

OS = Off-study
ND = Not done
* Dysphagia grade assessment rendered not evaluable; patient had esophageal stricture.

After the second course of PDT, 2 patients improved further at 1 week but none maintained that improvement at one month. 3/8 ((#5, 6, and 9) were improved at the second one month check compared to their original baseline grade.

6.1.5 Safety analysis

6.1.5.1 Deaths

18 patients have died and 1 was lost to followup. Median survival was 86 days with range 18 to 391 days.

Deaths are summarized in the Sponsor's table 13A, individual details are listed in table 13B (attached):

Table 13A. Number (Percentage) of Enrolled Patients Who Died, by Cause of Death

	PDT All		Tx-Related*
	No.	(%)	No.
No. Randomized	19	(100.0)	
No. Dead	18	(94.7)	2
Cause of Death			
Progressive Disease	11	(57.9)	1**
Metastatic PD	2	(10.5)	0
Unknown	1	(5.3)	0
Aspiration Pneumonia	1*	(5.3)	1
Pneumonia	1	(5.3)	0
Respiratory Failure	1*	(5.3)	0
Generalized Weakness	1	(5.3)	0

* Treatment-relationship assigned by the Investigator; includes events classified as definitely, probably and possibly related to treatment.

** Patient No. 2015/30 experienced numerous adverse events prior to death which the Investigator judged as probably or possibly related to treatment.

* Progressive disease was also listed as cause of death in the case report form.

Table 13B. Listing of Patients Enrolled Into Study Who Died

Pt. No./ Trial	Cause of Death	Treatment Relationship	Course	Days From Last Treatment Procedure	Procedure Type	Survival (days)	Off Study Reason
	PD	Remote	1	14	L	18	Death
	PD	Def Not	2	14	D	48	Death
	PD	Def Not	2	16	AD	153	Death
	PD	Def Not	1	16	L	19	Death
	PD Asp. Pneumo	**Poss**	**1**	**17**	**AD**	**27**	**Fistula/PD**
	PD	**Poss***	**2**	**30**	**D**	**86**	**Death**
	PD/ Resp. Fail.	Def Not	1	35	AD	42	PD
	Met PD	Def Not	2	38	D	86	Pt. Request
	Gen. Weakness	Remote	1	43	L	53	Pt. Deterioration
	PD	Def Not	1	61	D	68	Death
	PD	Def Not	1	94	L	102	Pt. Very Ill
	PD	Def Not	2	138	L	189	Fistula
	PD	Def Not	1	167	D	174	Failure to Achieve CR/PR
	PD	Def Not	1	214	D	218	Therapy Changed
	Pneumonia	Def Not	2	251	L	286	Protocol Completed
	PD	Def Not	2	336	D	391	Pt. Request
	Unknown	Def Not	NA	NA	NA	36	Laser Problems
	Met PD	Def Not	NA	NA	NA	36	Pt. Deterioration**

* Patient No. experienced numerous treatment-related adverse events prior to death.
* Patients not treated
** Patient No. had disease progression listed as off-study reason, but was terminated due to deterioration of condition secondary to brain metastasis.

D = Debridement
PD = Progressive Disease
L = Laser
AD = Assessment Debridement
Met = metastatic

In bold are the data from the 2 patients with deaths which were considered by the investigator to be possibly related to treatment.

6.1.5.2 Adverse Experiences

3 patients were removed from study for adverse experiences for fistula 118 days after treatment for fistula 16 days after treatment, and for deterioration from possible stroke (death on day 53).

11/17 (65%) of patients reported at least one severe (grade 3) or life-threatening (grade 4) adverse experience, but only three of these were considered by the investigator as treatment-related:

- Patient had perforation during dilatation 2 days after the second laser session. This resolved with treatment.
- Patient had a broncho-esophageal fistula 4 days after the last treatment procedure and died of aspiration pneumonia.
- Patient had worsening dysphagia 46 days after the last treatment which was attributed to treatment (perhaps this was stricture since there was no edema or necrotic tumor seen at endoscopy).

The 5 life-threatening events(occurring in 4 patients) are listed below:

- Pt. as noted above, died with aspiration pneumonia.
- Pt. died of respiratory distress and hypotension 16 days following treatment (cause of death is not clear).
- Pt. had dyspnea and CHF 2 days before death on day 16.
- Pt. had respiratory failure considered unrelated to therapy and resolved with treatment in 1 day.

Reviewer comments:

It is nearly impossible to sort out the contribution of treatment to the demise of these patients given their poor condition and the uncontrolled nature of this trial.

The individual categories of Grade 3 and grade 4 reactions are listed in the sponsor's table 13D:

Table 13D

Adverse Experience Summary (By Category/Adverse Experience)
Severe or Very Severe

	PDT			
	TOTAL		SEVERITY	
	N	%	SEV	VSEV
NUMBER OF PATIENTS	17	100.0		
At Least One Adverse Experience	11	64.7	7	4
Autonomic Nervous System	1	5.9		1
Hypotension	1	5.9		1
Psychiatric	1	5.9	1	
Anorexia	1	5.9	1	
Gastrointestinal	**4**	23.5	**4**	
Oesophageal Stricture	1	5.9	1	
Dysphagia	1	5.9	1	
Oesophageal Ulceration	2	11.8	2	
Vomiting	1	5.9	1	
Metabolic & Nutritional	1	5.9	1	
Dehydration	1	5.9	1	
Cardiovascular	**2**	11.8	**2**	
Cardiac Failure	2	11.8	2	
Heart Rate/Rhythm	1	5.9	1	
Fibrillation Atrial	1	5.9	1	
Respiratory	**8**	47.1	**4**	**4**
Bronchospasm	1	5.9	1	
Pneumonia	4	23.5	3	1
Respiratory Insufficiency	3	17.6		3
Tracheo-oesohageal Fistula	2	11.8	2	
Red Blood Cell	1	5.9	1	
Anaemia	1	5.9	1	
Body as a Whole	**5**	29.4	**5**	
Asthenia	1	5.9	1	
Chest Pain	1	5.9	1	
Fever	1	5.9	1	
Pain	2	11.8	2	

ADVERSE EXPERIENCE SELECTION: AT LEAST 'SEVERE' SEVERITY

As shown in by the reviewer 'bolding' of topics in table 13C, Grade 3 or Grade 4 reactions were most prominent in the Body as a Whole, Respiratory, and Cardiovascular systems.

All grades of adverse reactions which occurred in at least 20% of patients are listed by category in the sponsor's table 13C:

Table 13C.
Number (Percentage) of Treated Patients Reporting At Least One Adverse Event, by Body System, Individual Adverse Experience (Preferred Terms) Within Body System: Events For Which the Incidence is at Least 20%, Based on All Treated Patients

	PDT	
	No.	(%)
No. of Treated Patients	17	(100)
At Least One Adverse Experience	16	(94.1)
Type of Event		
All Psychiatric	6	(35.3)
All Gastrointestinal	**11**	**(64.7)**
Constipation	4	(23.5)
Nausea	4	(23.5)
All Respiratory	**11**	**(64.7)**
Pleural Effusion	4	(23.5)
Pneumonia	4	(23.5)
All Body as a Whole	**13**	**(76.5)**
Chest Pain	6	(35.3)
Fever	4	(23.5)
Pain	5	(29.4)

Treatment related events of all grades are listed in the sponsor's table 13 E. In bold I have highlighted general categories of events including 5 or more patients, or individual events which occurred in 3 or more patients.

Table 13E.
Number (Percentage) of Treated Patients Reporting At Least One Treatment-Related Adverse Event, by Body System and Individual Adverse Experience (Preferred Terms) Within Body System

	PDT	
	No.	(%)
No. of Treated Patients	17	(100)
At Least One Adverse Experience (Treatment-Related)	12	(70.6)
Type of Event		
All Skin and Appendages	3	(17.6)
Photosensitivity Reaction	3	(17.6)
All Autonomic Nervous System	1	(5.9)
Ileus	1	(5.9)
All Psychiatric	2	(11.8)
Anxiety	1	(5.9)
Insomnia	1	(5.9)
All Gastrointestinal	6	(35.3)
Abdominal Pain	2	(11.8)
Dysphagia	1	(5.9)
Eructation	1	(5.9)
Nausea	3	(17.6)
Esophageal Ulceration	2	(11.8)
Esophageal Ulceration Hemorrhage	1	(5.9)
Stomatitis Ulcerative	1	(5.9)
All Respiratory	6	(35.3)
Bronchospasm	1	(5.9)
Dyspnea	1	(5.9)
Pleural Effusion	2	(11.8)
Pneumonia	1	(5.9)
Hemoptysis	1	(5.9)
Pharyngitis	3	(17.6)
Tracheoesophageal Fistula	1	(5.9)
All Red Blood Cell	1	(5.9)
Anemia	1	(5.9)
All Body as a Whole	7	(41.2)
Back Pain	1	(5.9)
Chest Pain	3	(17.6)
Chest Pain Substernal	1	(5.9)
Fever	3	(17.6)
Rigors	1	(5.9)

Adverse reactions listed according to which 'formulation' of photofrin the patient received are listed in V. 1.40, p 219 of the NDA. 4 patients received the frozen formulation and 13 received the lyophilized formulation. The small number of patients who received the frozen formulation does not allow a formal comparison between groups, however Grade III or IV reactions occurred in 9/13 of the patients who received the Lyophilized drug versus 1/4 who received the frozen drug. All reactions are listed by grade below:

Events:	Grade: 0	I	II	III	IV	Total events	Patients
Frozen	-	-	3	1	-	4	4
Lyophilized	1	3	-	5	4	13	13

6.1.6 Applicant Summary and Conclusions

The summary and conclusions of the study report of P20 are on pp 166-178 of Volume 1.40. The following excerpts cover the most relevant points:

"Within each course of therapy, evaluations are restricted to the Week 1 and Month 1 visits, since the number of patients with data available for analysis beyond the Month 1 visit, within any course of therapy, is too small.

At baseline, the average dysphagia grade was 4.6 on a scale of 1 to 5. During the first course to therapy, the average dysphagia grade improved to a grade of 3 at both follow-up visits."

> "Objective response rates were assessed at both the Week 1 and Month 1 visits, during the first course of therapy. Response rate was 68% at the Week 1 assessment. At the Month 1 assessment the response rate decreased to 32%.
>
> In summary, based on efficacy criteria as defined for this study, it appears that PDT accomplishes debulking of tumor and temporary relief of symptoms. "

"Two deaths were considered treatment-related by the Investigator. One of these deaths occurred on Day 17 of Course one in a patient who had both progressive disease and aspiration pneumonia secondary to fistula formation. The second death occurred on Day 39 of Course two in a patient with a intramural perforation of the esophagus. The cause of death in this patient was reported to be progressive esophageal cancer. While it is impossible to disregard the attribution of death to PDT in these two cases, the difficulty of distinguishing treatment-related toxicities from the natural history of esophageal cancer in these patients must be acknowledged.

Three patients were removed from the study secondary to adverse events. Two patients were removed due to fistula formation and one was removed due to deterioration of condition attributed to a possible stroke."

"However, there were several severe and life threatening adverse events which may have impacted on the palliative effect of the therapy. These included respiratory, cardiac and gastrointestinal abnormalities. The cardiac and respiratory abnormalities may represent an as yet unreported locoregional toxicity of PDT.

The proportion of patients with at least one adverse event considered treatment-related was 71%. A high proportion of these treatment-related adverse events are mild to moderate in severity, occurring during the first cycle of therapy.

The investigators considered only three patients to have had severe or life threatening adverse events which were treatment-related. One patient had an esophageal perforation during a debridement endoscopy. The patient was placed on prophylactic antibiotics and recovered. A second patient developed a tracheoesophageal fistula, five days following the final treatment procedure of cycle one of treatment. The patient expired 12 days later due to aspiration pneumonia and progressive esophageal cancer. The third patient was reported to have severe, treatment-related dysphagia, 46 days following the last treatment procedure. However, there was no endoscopic evidence of PDT-related esophageal edema or tumor necrosis at that time."

"An extensive evaluation of changes in laboratory parameters including renal function tests, liver functions tests, and hematology tests is reported. There are only isolated abnormalities in laboratory tests attributed to PDT."

"In conclusion, Photodynamic Therapy with PHOTOFRIN® (porfimer sodium) is an active treatment for malignant dysphagia resulting from completely obstructing esophageal tumors. It provides temporary relief of dysphagia in a subpopulation of esophageal cancer patients who have no alternatives for palliative therapy. The incidence of endoscopic perforation of the esophagus appears similar to that observed with the thermal Nd:YAG laser used in patients with partially obstructing tumors. Other aspects of the safety profile of PDT may be of concern, particularly respiratory and cardiovascular events which are potentially attributable to a locoregional toxicity of Photodynamic Therapy. Further refinement of light dosimetry and/or drug dose may ameliorate these adverse effects and further enhance the utility of this new palliative modality."

6.1.7 Reviewer's summary and Conclusions on Study P20

Despite inclusion of 32 centers in this study, only 17 eligible patients were accrued over about 3 1/2 years. 12 patients had grade 5 dysphagia at baseline. 17 patients were treated. 13 received the lyophilized formulation and 4 the frozen formulation. 12 of the patients had received prior therapy. Seven of the eligible patients (completely obstructed) had a subjective improvement at one month followup, although one of these experienced esophageal perforation. The changes in dysphagia grades of the other 6 dysphagia responders are listed below to allow clinical correlation of change in grade with clinical meaning of such a change:

Dysphagia Responses; Clinical meaning of 1-month data

Grades of Dysphagia Defining symptoms	# of Pdt Responders:	1	1	1	3	Total = 6
Patient can swallow:	Dysphagia Grade					
All *solids.*	1					
Some *solids.*	2	X	X			
No *solids; liquids* without difficulty.	3	↑	↑	X		
Liquids with difficulty.	4	↑	↑	↑	X	
No *liquids.*	5		↑	↑	↑	

This chart outlines the major subjective benefit measured in the 17 patients with completely obstructing esophageal cancer. The physical finding of a patent lumen at one month (objective response) was also noted in most of these subjective responders.

Safety analysis was difficult in this small non-comparative study of patients who have a very poor short-term prognosis with or without treatment. Investigators considered 2 deaths to be treatment related. 11/17 patients were considered to have at least one severe (grade 3) or life-threatening (grade 4) experience, but only 3 were considered by investigators to be treatment-related. The most common events involved the GI or Respiratory systems or were more general (such as pain, chest pain, or fever).

In conclusion this study suggests that 6/17 (35%) of patients with completely obstructed esophageal cancer demonstrated some symptomatic improvement and objective response one month after therapy with photofrin. An examination of the uncontrolled safety data suggests that the toxicity profile is similar to that seen in the larger controlled study of patients with partially-obstructing disease. Whether the balance of efficacy to toxicity shown in this patient group is favorable enough to warrant NDA approval is an issue which should be decided in conjunction with advice from the Oncology Drugs Advisory Committee.

Addendum: the above analysis was done on the basis of the P20 study report and review of the data submitted in electronic form. The reader is also referred to the review of the graphical presentation of data from this study found in the review of the Applicant's Summary of Efficacy in the next section of this review.

7.0 Review of Applicant's Integrated Summary of Efficacy:

Introductory Reviewer Comments

Medical Officer Review #1 concentrated on the efficacy and safety data of the largest study (P19 in partially obstructing esophageal cancer) as it was reported in the Applicant's Final Study Report and as analyzed by the reviewer from the electronic data submitted by the applicant. The the integrated summary of efficacy located in volume 42 of the NDA is the subject of this section of Medical Officer Review #2. In addition to overview analyses and tables of analyses done in the individual studies, the sponsor also presents some new ways of viewing data on primary patients.

In this section of MOR#2 the FDA reviewer wishes to accomplish several purposes:

- to document several of the applicant's summary tables for reference.
- to discuss new analyses of the efficacy data presented by the sponsor.
- to present the applicant's summary and conclusions.

Much of this section will represent verbatim tables and text prepared by the applicant in the 150-page efficacy summary. Interspersed will be reviewer comments and conclusions. Special attention should be given to the sponsor's presentation of "Patients with a Clinically Important Benefit from PDT." This presents a graphical attempt to portray risk and benefit of selected patients and was not part of the P19 study report.

7.1 Overview Tables

Details of design and enrollment of the 2 major studies in esophageal cancer, P19 and P20 are nicely summarized in attached table 1.

Table 2 summarizes other studies in the NDA from literature describing findings in a total of 182 patients.

TABLE 2. Other Sources of Efficacy Data for PDT in Esophageal Cancer

Patient Population	Number of References	Number of Patients
Superficial (early) carcinoma	5	76
Partially obstructing carcinoma	4	53
Partially obstructing carcinoma (EDR)[a]	1	51
Completely obstructing carcinoma	1	2
TOTAL	11	182

[a] Patients treated in Canada under the Emergency Drug Release (EDR) Program

TABLE 1. Adequate and Controlled Studies

Protocol Number	Enrollment Start and Stop Dates	Location	Study Design	Treatment Dose	Number Entered Each Treatment	Age Range (Median)	Gender Race No. (%)		NDA Location (Volume/Page)
P19	Start date: 9/16/88 Stop date: 8/6/92	US and Canada 32 trial sites initiated 24 trial sites enrolled at least 1 patient	Phase III, open-label multicenter, randomized, comparative trial (PDT versus Nd:YAG) in patients with partial esophageal obstruction	PDT with PHOTOFRIN at 2.0 mg/kg and total 630-nm-light dose of 300 J/cm versus	PDT 118 enrolled 110 treated	36-99 (68)	Men: Women: Caucasian: Black: Asian: Hispanic:	89 (75) 29 (25) 99 (84) 15 (13) 3 (3) 1 (1)	
				Nd:YAG 500-30,000 Joules	Nd:YAG 118 enrolled 108 treated	50-96 (72)	Men: Women: Caucasian: Black: Hispanic:	80 (68) 38 (32) 106 (90) 8 (7) 4 (3)	
P20	Start date: 4/13/89 Stop date: 8/25/92	US and Canada 32 trial sites initiated 8 trial sites enrolled at least 1 patient	Phase III, single-arm, multicenter trial in patients with complete esophageal obstruction	PDT with PHOTOFRIN at 2.0 mg/kg and total 630-nm-light dose of 300 J/cm	PDT 19 enrolled 17 treated	41-86 (68)	Men: Women: Caucasian: Black:	10 (53) 9 (47) 15 (79) 4 (21)	

Tables 12, 13 and 15 provide useful summaries of data on dysphagia grades and response based on change in dysphagia grade as analyzed in study reports and reviewed earlier in this review and in MOR #1.

Tables 18-21 represent useful new analyses by the sponsor, similar to a reviewer-analysis in MOR #1. As noted earlier, when patients remained onstudy to give a dysphagia report, more patients showed improvement than showed worsening.

The Sponsor's assessment of objective response is summarized in table 26.

TABLE 12. Course 1 Dysphagia Grades and Changes From Baseline All Evaluable Data

TABLE 12. Course 1 Dysphagia Grades and Changes From Baseline

All Evaluable Data

Visit	P19			P20
	PDT	Nd:YAG	Difference (PDT-Nd:YAG)	PDT
BASELINE				
Mean dysphagia grade (n)[a]	2.87 (113)	2.90 (116)		4.63 (19)
WEEK 1				
Mean dysphagia grade (n)[a]	2.17 (87)	1.89 (89)		3.14 (14)
Mean change (n)[b]	-0.80 (83)	-1.01 (87)	0.22	-1.50
[95% CI[c]-mean change]	[-1.05, -0.54]	[-1.23, -0.80]	[-0.12, 0.55]	[-2.20, -0.80]
MONTH 1				
Mean dysphagia grade (n)[a]	2.09 (74)	2.11 (63)		3.38 (8)
Mean change (n)[b]	-0.75 (69)	-0.74 (61)	-0.02	-1.25
[95% CI[c]-mean change]	[-1.04, -0.46]	[-1.01, -0.47]	[-0.42, 0.38]	[-1.97, -0.53]
MONTH 2				
Mean dysphagia grade (n)[a]	2.58 (26)	2.30 (20)		3.67 (3)
Mean change (n)[b]	-0.13 (24)	-0.40 (20)	0.27	-1.00 (3)
[95% CI[c]-mean change]	[-0.44, 0.19]	[-0.61, -0.19]	[-0.44, 0.92]	[d]

[a] (n) represents the number of patients with evaluable assessments at this visit.

[b] Negative changes indicate improvements from baseline, positive changes indicate worsening. (n) represents the number of patients with evaluable assessments both at this visit and at baseline.

[c] CI = Confidence Interval, adjusted using O'Brien-Fleming Procedure for the between-group comparison to reflect the interim analysis

[d] Too few patients

TABLE 13. Course 1 Response Assessments Based on Improvement in Dysphagia Grades

Intent-to-Treat Analysis

Number (%) of Patients

Response Category	P19 PDT n=118		P19 Nd:YAG n=118		P20 PDT n=19	
RESPONDERS[a]						
Any assessment[b]	65	(55)	64	(54)	13	(68)
Week 1	52	(44)	57	(48)	12	(63)
Month 1	41	(35)	34	(29)	8	(42)
Week 1 and Month 1	28	(24)	27	(23)	7	(37)
NONRESPONDERS	38	(32)	35	(30)	4	(21)
NOT EVALUATED	15	(13)	19	(16)	2	(11)

[a] Patients with improved dysphagia grades
[b] Patients with improved response at Week 1 or Month 1

TABLE 15. Month-1 Response Based on Improvement in Dysphagia Grades by Baseline Grade

All Available Data

Number[a]/Total[b] (%) of Patients

Baseline Dysphagia Grade	P19						P20	
	PDT		Nd:YAG		Difference[c] (PDT-Nd:YAG)		PDT	
1	0/2	(0)	0/4	(0)	(0)		0	(0)
2	11/52	(21)	7/49	(14)	(7)		0	(0)
3	10/28	(36)	7/23	(30)	(6)		0	(0)
4	19/32	(59)	20/40	(50)	(9)		2/7	(29)
5	1/4	(25)	0/2	(0)	(25)		6/12	(50)

[a] Number of patients who had an improvement in dysphagia grade
[b] Number of patients with specific dysphagia grade at baseline
[c] Difference in percentage response rates

TABLE 18. Baseline to Month-1 Change in Dysphagia Grades in Study P19 (PDT)

Baseline Dysphagia Grade	Change in Dysphagia Grade at Month 1 with PDT									
	Worsening in Dysphagia			No Change	Improvement in Dysphagia					
	3 Grades	2 Grades	1 Grade	0	1 Grade	2 Grades	3 Grades	4 Grades	Missing	Total
1	0	0	0	1	0	0	0	0	1	2
2	1	0	0	21	11	0	0	0	19	52
3	0	1	4	4	6	4	0	0	9	28
4	0	0	0	2	8	5	6	0	11	32
5	0	0	0	0	0	0	0	1	3	4
TOTAL	1	1	4	28	25	9	6	1	43	118

TABLE 19. Baseline to Month-1 Change in Dysphagia Grades in Study P19 (Nd:YAG)

Baseline Dysphagia Grade	Change in Dysphagia Grade at Month 1 with Nd:YAG									
	Worsening in Dysphagia			No Change	Improvement in Dysphagia					
	3 Grades	2 Grades	1 Grade	0	1 Grade	2 Grades	3 Grades	4 Grades	Missing	Total
1	0	1	1	2	0	0	0	0	0	4
2	0	0	2	18	7	0	0	0	22	49
3	0	0	2	3	4	3	0	0	11	23
4	0	0	1	4	6	11	3	0	15	40
5	0	0	0	0	0	0	0	0	2	2
TOTAL	0	1	6	27	17	14	3	0	50	118

TABLE 21. Baseline to Month-1 Change in Dysphagia Grades in Study P20

Baseline Dysphagia Grade	Change in Dysphagia Grade at Month 1 with PDT									
	Worsening in Dysphagia			No Change	Improvement in Dysphagia					
	3 Grades	2 Grades	1 Grade	0	1 Grade	2 Grades	3 Grades	4 Grades	Missing	Total
4	0	0	0	2	1	1	0	0	3	7
5	0	0	0	0	3	1	1	1	6	12
TOTAL	0	0	0	2	4	2	1	1	9	19

TABLE 26. Number of Patients Responding During Course 1 Based on Objective Tumor Response

	Number (%) of Patients	
	P19	P20
Response Category		

	PDT n = 118	Nd:YAG n = 118	PDT n = 19
RESPONDERS[a]			
Any assessment[b]	61 -52	52 -44	16 -84
Week 1	53 -45	47 -40	14 -74
Month 1	38 -32	24 -20	6 -32
Week 1 and Month 1	30 -25	19 -16	4 -21
NONRESPONDERS	32 -27	33 -28	1 -5
NOT EVALUATED	25 -21	33 -28	2 -11

[a] Patients with objective tumor responses (partial or complete response)
[b] Patients with response at Week 1 or Month 1

7.2 Review of Applicant's Graphical Overview of Patients with Important Benefit.

Comments on Graphical Patient Histories presented in the NDA Summary of Efficacy and in ODAC overview documents:

The Applicant has presented very instructive graphical overviews of the clinical course of individual patients whom the applicant has selected as having "responded very favorably with minimal adverse reactions" in study P19 and P20. Th se are instructive in helping us assess whether there is a group of patients that seem to have experienced net benefit compared to no treatment.

The sponsor's Table 40 (attached) summarizes the demographic information on the 32 patients from the 2 studies whom the sponsor described as showing net benefit in these graphical analyses. The sponsor's table 41 demonstrates the sponsor's criteria for selection: Complete response, achievement of Grade 1 dysphagia, or improvement by 2 or more grades in dysphagia assessment with minimal adverse reactions.

TABLE 40. Baseline Characteristics of Patients With a Clinically Important Benefit From PDT

Number (%) of Patients

	P19				P20			
	Select Subset of Responders (n=20)		Remaining Treated Patients (n=90)		Select Subset of Responders (n=11)		Remaining Treated Patients (n=6)	
Gender								
Men	12	(60	71	(79	5	(45	3	(50
Women	8	(40	19	(21	6	(55	3	(50
Age								
<60	2	(10	23	(26	2	(22	0	0
≥60	18	(90	67	(74	9	(82	6	(100
Tumor Histology								
Squamous cell carcinoma	9	(45	41	(46	7	(64	1	(17
Adenocarcinoma	11	(55	47	(52	4	(36	5	(83
Other	0	0	2	(2	0	0	0	0
Tumor Location in the Esophagus								
Upper third	3	(15	18	(20	6	(55	2	(33
Middle third	8	(40	37	(41	3	(27	3	(50
Lower third	9	(45	33	(37	2	(18	1	(17
Unknown	0	0	2	(2	0	0	0	0
Tumor Length (cm)								
≤5	13	(65	38	(42	2	(18	0	0
-3	4	(20	37	(41	1	(9	2	(33
≥10	3	(15	13	(14	2	(18	1	(17
Unknown	0	0	2	(2	6	(55	3	(50
Prior Therapy								
Yes	4	(20	48	(53	8	(73	2	(33
No	16	(80	42	(47	3	(27	4	(67

TABLE 41. Efficacy Results For Patients With a Clinically Important Benefit From PDT

	Number of Patients	
	P19	P20
Number of Patients	20	11
Treatment Efficacy[a]		
Complete tumor response	5	3
Achieved dysphagia Grade 1[b]	14	2
Dramatic dysphagia improvement[c]	1	6
Duration of Benefit (days)		
Median	107	69
(Range)		

[a] Patients are summarized by greatest response in the following order: complete response > dysphagia Grade 1 > dramatic dysphagia improvement

[b] Able to swallow all solids without difficulty

[c] Improvement of baseline dysphagia by two grades or more

There are 22 cases for Study P19 and 9 cases for P20. The reviewer reviewed the graphical presentations and prepared the following notes and rating for each case. An ad hoc rating scale was used in this review. Notes refer primarily to dysphagia grades:

Reviewer rating scale for assessing benefit in Sponsor's 'Graphic Presentation of Efficacy and Safety' for selected Patients in Study P19 and P20:

Rating		Criteria
1	No Significant benefit proved	
2	Some Benefit	Mod Benefit, short duration
3	Marked benefit	Mod Benefit, long duration or Large benefit,
4	Extreme benefit	Large benefit, long duration (>2mo)
5	Exceptional benefit	Large benefit, very long duration (6 months)

Study P19:

Patient	My Assessment	Reviewer Rating
	Grade 4 to 1-2 for 50+ days	4
	4 to 2 for 20+ days. Tox G3 at day 30	2
	5 to 1 for 50+ days (more second Rx)	4
	4 to 1 for 20 days; death day 35	2
	3 to 1 for 120 days, early TEF G4, 2 Rxs.	3
	4 to 1 for 60+ days, G2 tox d 40.	4
	2 to 1 for 150+ days.	3
	2 to 1 for 70+ days.	2
	4 to 1 20+ days, 3 at d70 to 2 at d 50+.	3
	4 to 1, 30 d, then 5 to 1 for 30d.	3
	3 to 2 for 190 d; to 1 for 20 d at 2 times.	4
	2 to 1 to 2, CR after course 2 for 80+ days	3
	3 to 1 to 2 over 3 treatments, 100 +	3
	4 to 2 course 1, 2 to 1 course 2. 1 at d 180 2 at day 270	4
	2 to 1 to 2 but CR on d 95. Much tox.	1
	3 to 1 for 140+ d.	4
	2 to 1 for 30+ d. CR.	2
	4 to 2, 40 + d, 2 Rx.	3
	3 to 2 130 + d with 2 Rx.	3
	2 to 1 to 3 (stricture withCR) to 1 on d 200.	3
	5 to 2 to 4 out to 140+ d, 2 courses.Much tox.	3
	4 to 2 30 d, to 4 dilated, to 2 80+d.	3

Study P20

1	No Significant benefit proved	
2	Benefit	Mod Benefit, short duration
3	Marked benefit	Mod Benefit, long duration or Large benefit, short dur.
4	Extreme benefit	Large benefit, long duration (>2mo)
5	Exceptional benefit	Large benefit, very long duration (6 months)

Patient	My Assessment	Reviewer Rating
	5 to 3 on day 13. Progression 4 d later.	2
	4 to 2 on day 18, with CR.	2
	4 to 3 on d 20 to 28. deteriorate d 28.	2
	5 Esoph perf d 8. 1 on d42.	3
	5 to 4 to 3 d 30	3
	5 to 2 for 60+d.	4
	5 to 1 to 4 to 1 to 4 to 3; 3 courses.	3
	4 to 3 (60 d over 2 courses) to 4 with CR.	2
	4 to 3 to 4 to 2, reRx, to 3 to 4. Short dur.	2

The summary of reviewer rating of benefit of these 32 patients is outlined below.

Study P19

Total No. Pos Risk/Ben 22
Total No. Patients 118

Benefit Scale	# Patients
1	1
2	4
3	11
4	6
5	

Study P20

Benefit Scale	# Patients
Total No. Pos Risk/Ben	9
Total No. Patients	19
1	
2	5
3	3
4	1
5	

Reproduced in the appendix of this review are copies of the applicant's graphical presentation of data on 10 patients (These are patients that the reviewer rated as 4 or above in study P19 and 3 or above in study P20).

Reviewer Concluding Comments on Graphical Presentation of Efficacy/Toxicity data:

I do think this is a useful technique for attempting to make a patient-by-patient judgment about the balance of efficacy and toxicity for individual patients. In my opinion this is most useful for study P20, for completely obstructing cancer, where there is no other acceptable therapy. In this case the question is whether there is net benefit enough patients to warrant approval for this rare indication. With P19 our main question is not whether any patients get benefit in excess of toxicity, but whether there is excess toxicity in comparison to YAG; and if so, is does the magnitude of this excess toxicity outweigh any potential advantages of PDT over YAG. In that circumstance, statistical comparisons of toxicity as documented in the randomized study should be emphasized rather than individual case histories.

7.3 Efficacy by subsets:

On pp 125-147 of V 42 the sponsor analyses efficacy data for the following subsets: Age, Gender, Histology, Prior treatment, Submucosal tumor, Tumor location, Tumor length, and Formulation (frozen vs lyophilized). Except for tumor location and length no associations were claimed.

Both therapies were less effective in patients with upper esophageal lesions.

The following are the sponsor's comments from the efficacy summary with attached tables 52-54 from that summary:

Sponsor's comments regarding tumor location:

"Both therapies were less effective in reducing dysphagia associated with tumors in the upper third of the esophagus. PDT therapy was less effective than Nd:YAG in reducing dysphagia with tumors located in the upper third at the Week-1 assessment, possibly due to edema. At the Month-1 evaluation, the two therapies achieved the same level of dysphagia improvement.

Based on objective response (Table 53), there is a tendency for PDT-treated patients with tumors in the upper or lower third of the esophagus to have better response than Nd:YAG-treated patients at both Week 1 and Month 1. The two therapies were equally effective with tumors in the middle third."

"Treating tumors in the upper third of the esophagus is difficult with Nd:YAG therapy because it is hard to maneuver the fiber tip in this narrow region. Also, the patients are uncomfortable from the sensation of pressure and fullness in the throat caused by the insufflation of carbon dioxide; the trachea is immediately beneath the cervical esophagus. The patients become agitated and do not lay still, further complicating the delivery of Nd:YAG therapy. In lower-third lesions, angulation at the esophagogastric junction and technical problems associated with movement in this area (such as heart palpitations, respiratory movements and peristalsis contractions) make Nd:YAG treatments difficult in this region. PDT is technically easier as it only requires the endoscopic placement of a fiber optic diffuser, prior to switching on the laser for the required treatment time and is less affected by patient motion. The improved objective response with PDT for tumors in the upper and lower third of the esophagus is clinically important, as one-half of esophageal carcinoma are located in these regions(2)."

Sponsor's comments regarding response according to tumor length:

"For tumors equal to or greater than 10 cm in length at baseline, PDT-treated patients tended to have superior response rates compared to Nd:YAG-treated patients at both Week 1 (44% versus 22%) and Month 1 (38% versus 11%), although the 95% confidence intervals overlap zero. For tumors of intermediate length (6-9 cm), Nd:YAG therapy tended to result in a greater objective response rate than did PDT therapy, consistent with the trend seen in dysphagia improvement. For small tumors (<5 cm), PDT appeared to elicit a greater response."

TABLE 52. Course 1 Subset Presentation of P19 Dysphagia Analysis by Tumor Location

All Available Data

Number (%) of Patients

Visit	Upper Third			Middle Third			Lower Third		
	PDT	Nd:YAG	Difference*	PDT	Nd:YAG	Difference*	PDT	Nd:YAG	Difference*
BASELINE									
n	23	29		47	49		44	37	
Mean dysphagia grade	2.87	2.93		2.94	2.98		2.80	2.81	
WEEK 1									
n	18	24		37	37		37	31	
Mean dysphagia grade	2.72	2.00		2.08	1.78		2.05	2.13	
Mean change	-0.17	-0.83	0.67	-1.00	-1.16	0.16	-0.76	-0.74	-0.01
[95% CI on mean]	[-0.74, 0.41]	[-1.22, -0.45]	[-0.03, 1.37]	[-1.36, -0.64]	[-1.54, -0.79]	[-0.37, 0.69]	[-1.15, -0.36]	[-1.12, -0.37]	[-0.57, 0.54]
MONTH 1									
n	12	16		32	27		31	25	
Mean dysphagia grade	2.00	2.31		2.16	2.15		2.06	2.12	
Mean change	-0.42	-0.5	0.08	-0.91	-0.78	-0.13	-0.71	-0.68	-0.03
[95% CI on mean]	[-0.98, 0.15]	[-1.01, 0.01]	[-0.68, 0.85]	[-1.32, -0.49]	[-1.20, -0.35]	[-0.73, 0.47]	[-1.16, -0.26]	[-1.11, -0.25]	[-0.66, 0.60]

* Difference in response rates (PDT-Nd:YAG)

TABLE 53. Course 1 Subset Presentation of P19 Objective Tumor Response by Tumor Location

Intent-to-Treat Analysis

Number (%) of Patients

	Upper Third			Middle Third			Lower Third		
Visit	PDT	Nd:YAG	Difference[a]	PDT	Nd:YAG	Difference[a]	PDT	Nd:YAG	Difference[a]
WEEK 1									
n	23	29		47	49		44	37	
CR + PR	12 -52	11 -38	-14	17 -36	20 -41	(-5)	24 -55	16 -43	-11
[95% CI][b]			[-14, 41]			[-24, 15]			[-11, 33]
SD + PD	6 -26	8 -28		15 -32	10 -20		11 -25	9 -25	
Missing	5 -22	10 -34		15 -32	19 -39		9 -20	12 -32	
MONTH 1									
n	23	29		47	49		44	37	
CR + PR	9 -39	4 -14	-25	11 -23	12 -24	(-1)	18 -41	8 -22	-19
[95% CI][b]			[2, 49]			[-18, 16]			[-1, 39]
SD + PD	3 -13	9 -31		16 -34	12 -24		12 -27	12 -32	
Missing	11 -48	16 -55		20 -43	25 -51		14 -32	17 -46	

[a] Difference in response rates (PDT-Nd:YAG)
[b] 95% Confidence Interval on rate of response

TABLE 54. Course 1 Subset Presentation of P19 Dysphagia Grade Analysis by Tumor Length

All Available Data

Visit	≤ 5 cm			6 to 9 cm			≥ 10 cm		
	PDT	Nd:YAG	Difference[a]	PDT	Nd:YAG	Difference[a]	PDT	Nd:YAG	Difference[a]
BASELINE									
n	55	67		43	29		16	18	
Mean dysphagia grade	2.84	2.82		2.88	2.97		2.94	3.00	
WEEK 1									
n	45	60		33	22		14	10	
Mean dysphagia grade	2.04	2.08		2.33	1.68		2.36	1.90	
Mean change	-0.84	-0.73	-0.11	-0.64	-1.32	0.68	-0.64	-1.00	0.36
[95% CI on mean]	[-1.19, -0.50]	[-1.03, -0.44]	[-0.57, 0.35]	[-1.10, -0.17]	[-1.75, -0.88]	[0.04, 1.32]	[-1.17, -0.11]	[-1.51, -0.49]	[-0.38, -1.10]
MONTH 1									
n	40	40		26	22		9	5	
Mean dysphagia grade	1.92	2.05		2.31	2.23		2.22	2.60	
Mean change	-0.85	-0.60	-0.25	-0.50	-0.86	0.36	-1.00	-0.60	-0.40
[95% CI on mean]	[-1.22, -0.48]	[-0.96, -0.24]	[-0.77, 0.27]	[-0.99, -0.01]	[-1.30, -0.43]	[-0.30, 1.02]	[-1.65, 0.35]	[-1.38, 0.18]	[-1.43, 0.63]

[a] Difference in response rates (PDT-Nd:YAG)

Reviewer comments:

While suggestive, these subset analyses can only be considered exploratory and need verification.

Formulation (frozen or lyophilized) showed no difference in objective response. As shown in the sponsor's table 56, dysphagia grades favored the frozen formulation at 1 week but not at one month:

TABLE 56. Course 1 Subset Presentation of Dysphagia Analysis by PHOTOFRIN Formulation

All Available Data

Visit	P19		
	Frozen	Lyophilized	Difference[a]
BASELINE			
n	43	67	
Mean dysphagia grade	3.07	2.78	
WEEK 1			
n	33	60	
Mean dysphagia grade	2.03	2.32	
Mean change	-1.15	-0.5	-0.65
[95% CI on mean change]	[-1.62, -0.68]	[-0.77, -0.23]	[-1.20, -0.11]
MONTH 1			
n	29	46	
Mean dysphagia grade	2.07	2.11	
Mean change	-0.93	-0.63	-0.3
[95% CI on mean change]	[-1.45, -0.41]	[-0.92, -0.34]	[-0.91, 0.31]

[a] Difference in response rates (frozen-lyophilized)

Reviewer comments:

Again this is an exploratory subset analysis of a retrospective non-randomized comparison in one arm of a study. The 1-week finding could be suggestive of a physiological difference, but the one month finding, which I consider more clinically significant, and the objective findings do not suggest that a difference in efficacy has been demonstrated between Frozen and Lyophilized formulations.

Sponsor's Discussion and Conclusions from Integrated Summary of Efficacy:

The sponsor's 6 pages of comments and conclusions from the Integrated Summary of Efficacy (pp 154-160, volume 1.42) are reproduced for consideration:

"DISCUSSION

Palliation of dysphagia is an integral part of the therapy of esophageal carcinoma. For patients with completely obstructing tumors, no other palliative treatments are available. In patients with partial obstruction, a variety of treatment modalities are currently employed, including surgical resection, external beam radiotherapy, combination chemotherapy, mechanical dilatation, esophageal intubation, and thermal ablation of tumor with the Nd:YAG laser (2). In appropriately selected patients, these all offer temporary relief of symptoms. Among the available therapies for patients with partial tumor obstruction, Nd:YAG laser is considered the standard against which any new palliative treatment should be compared (5). For this reason, Nd:YAG laser therapy was chosen as the comparative modality for the comparative P19 study.

Like any surgical procedure, the outcome of Nd:YAG laser therapy for esophageal carcinoma is partially dependent on the experience of the endoscopist. The therapy is not selective for the tumor and carries a risk of local toxicities, the most serious being esophageal perforation (5,32). Furthermore, prior therapy for esophageal cancer, particularly radiation therapy, results in a flat and infiltrating tumor morphology with accompanying fibrosis. The Nd:YAG laser is less successful in treating this tumor morphology than bulky, intraluminal disease. PDT with PHOTOFRIN is a selective therapy. PDT does not employ a thermal laser but rather utilizes the selective retention properties of PHOTOFRIN combined with the ease of laser fiber optic placement to cause local, selective tumor destruction.

This Integrated Summary of Efficacy presents data from two adequate and well-controlled clinical studies. Study P19 demonstrates that PDT with PHOTOFRIN is comparable to or better than the Nd:YAG laser in its ability to reduce esophageal obstruction due to tumor and comparable in its ability to palliate dysphagia due to esophageal cancer. Another study, P20, demonstrated the effectiveness of PDT with PHOTOFRIN in patients with completely obstructing esophageal tumors.

A total of 255 patients were enrolled into the two prospective trials. The studies met the requirements of adequate and well-controlled studies as defined by the Code of Federal Regulations.

The majority of patients, whether treated with PDT or Nd:YAG, laser were removed from study due to disease progression or death secondary to disease progression. The high death rate was not unexpected in this aggressive disease and was comparable in the PDT- and Nd:YAG-treated groups. In addition, endoscopic assessments were sometimes not performed in these very ill patients.

In Study P19, analyses of all available Course 1 efficacy data from patients randomized to PDT with partial esophageal obstruction show PDT results in:

- a mean change (improvement) in dysphagia grade (from a baseline of Grade 3) of 0.73 at Week 1 (n=93) and 0.75 at Month 1 (n=75),
- a response rate, based on dysphagia grade improvement, of 55% at any assessment, 44% at Week 1, 35% at Month 1, and 24% at both Week 1 and Month 1,
- an objective tumor response rate (CR + PR) of 52% at any assessment, 45% at Week 1 and 32% at Month 1, and 25% at both Week 1 and Month 1
- a median time to palliation failure of 34 days,
- a median time to treatment failure of 35 days, and
- a mean change (increase from baseline) in esophageal lumen diameter (from a mean baseline of 0.7 cm) of 0.4 cm at Week 1, and 0.3 cm at Month 1.

PDT and Nd:YAG were equivalent in improving dysphagia. During the first course, objective response rates at Week 1 were similar for the two therapies (PDT 45%; Nd:YAG 40%). However at the Month-1 assessment, the response rate for the PDT group (32%) was statistically superior to the Nd:YAG group (20%).

Analyses of objective response by patient subset suggests that PDT may be superior to Nd:YAG for patients with tumors located in the upper or lower third of the esophagus, with tumors >10 cm or <5 cm in length and for patients who had received any prior therapy for their esophageal cancer. The improved objective response with PDT for tumors in the upper and lower third of the esophagus is clinically significant, as one-half of esophageal carcinomas are located in these regions (2). Furthermore, 15% of esophageal tumors present in the cervical (upper third) esophagus, where Nd:YAG therapy is less successful (31,32).

No difference in KPS was seen in either group following treatment. This was not unexpected in this patient population, as both PDT and Nd:YAG represent local palliative therapies.

Patients in the PDT and Nd:YAG groups had comparable survival rates and survival durations. Eighty-seven percent of patients in the PDT group and 86% of patients in the Nd:YAG group died. The median duration of survival (Kaplan-Meier estimate) was 123 days for patients randomized to PDT and 140 days for patients randomized to Nd:YAG. The hazard ratio was 0.97.

In Study P20, among all available data from the 19 PDT patients who presented with complete esophageal obstruction due to tumor, the following Course 1 results documented the efficacy of PDT with PHOTOFRIN:

- a mean change (improvement) in dysphagia grade (from a mean baseline grade of 4.6) of 1.4 grades at Week 1 (n=17), and 1.5 at Month 1 (n=10) following Course 1,
- a response rate based on dysphagia grade improvement of 68% at any assessment, 63% at Week 1, 42% at Month 1, and 37% at both Week 1 and Month 1,
- an objective tumor response rate (CR + PR) of 74% at Week 1, and 32% at Month 1,
- a median time to palliation failure of 30 days,
- a median time to treatment failure of 30 days, and
- a mean change (increase from baseline) in esophageal lumen diameter of 0.60 cm at Week 1, and 0.60 cm at Month 1.

Ninety-five percent of Study P20 patients died. Median patient survival duration was calculated to be 86 days.

At both Week 1 and Month 1, the improvements seen in dysphagia and the objective response rates are clinically significant in this population of patients where no other acceptable treatment options are available.

A second course of PDT therapy was of clinical benefit to many patients treated. Effectiveness, as measured by the same clinical endpoints as for Course 1, was comparable between the PDT- and Nd:YAG-treated patients in Study P19. In Study P19, where 42 PDT and 47 Nd:YAG-treated patients received a second course of therapy, dysphagia grade improved by 0.4 to 0.6 grades at the Week-1 evaluation following Course 2. Some 43% of PDT and 26% of Nd:YAG-treated patients showed improvement in dysphagia grade at any follow-up assessment.

When all courses of therapy are considered, a total of 12 PDT-treated patients achieved a complete response, 9 in Study P19 and 3 in Study P20. One-quarter of these patients achieved responses of clinically significant duration. Two patients in Study P19 achieved a complete response at Month 2 during Course 1 that was maintained at subsequent assessments up to and including Month 6. Two additional patients (one in Study P20) achieved a complete response by Month 1 of Course 2 that was maintained for the duration of the 6-month follow-up. Furthermore, 7 of the 12 patients achieved a complete response that was supported by negative microscopic evidence of esophageal malignancy. Two patients treated with Nd:YAG achieved a complete response, but the duration was limited to Week 1 in one patient and occurred only at Month 6 in the other.

The number of interventions with PDT and Nd:YAG therapies is significant from a quality-of-life standpoint. Patients treated with PDT required an average of 2.1 endoscopies in Course 1 compared to 2.8 endoscopies for those treated with Nd:YAG. Typically, a course of PDT consists of an injection of PHOTOFRIN as an outpatient procedure, followed 2 days later by the first of one or two endoscopies at which nonthermal laser light is applied to the tumor via optical fibers. Necrotic tumor may be debrided at a subsequent endoscopy. Nd:YAG laser therapy consists of multiple sessions using a unselective thermal process that may require three or more endoscopies, with repeated courses every 4-6 weeks.

Both PDT and Nd:YAG therapies are designed to remove tumor mass. In these two studies, objective tumor response was felt to be the best available assessment of the ability for each of these modalities to reduce obstruction due to tumor mass. However, as originally defined in the protocol, objective tumor response included the measurement of tumor size, through endoscopic assessment of the tumor length and its cross-sectional dimensions. Accurate cross-sectional measurements were difficult to obtain and were not available for a large number of patients. Therefore, objective response was redefined to reflect changes in luminal diameter.

From the patient's perspective, dysphagia is the most important endpoint, but has its own limitations for efficacy analysis. The five-point dysphagia scale, while indicating milestones that are significant for the patient (e.g., being able to swallow solids without difficulty), is a subjective evaluation. Furthermore, results from these studies suggest a relative lack of linearity in this scale, as indicated by the ease with which both PDT and Nd:YAG were able to obtain greater palliation in patients with higher baseline scores. The degree of dysphagia is also influenced by several factors in addition to luminal obstruction, such as esophageal compression from extrinsic tumor, and abnormalities in peristaltic action caused by fibrosis from prior X-ray therapy or submucosal tumor involvement.

Objective response (i.e., reducing esophageal obstruction) is necessary but not always sufficient to ensure improvement in dysphagia. Study P19 indicates PDT is at least as good as Nd:YAG in reducing esophageal obstruction. Some subset analyses show that in fact, PDT may be superior for reducing esophageal obstruction to Nd:YAG for selected tumor characteristics. However, the advantages for PDT indicated with objective response did not translate into the anticipated improvement in dysphagia. The results for dysphagia show equivalent improvement for both therapies.

The limitations of Nd:YAG therapy are apparent for lesions in the upper and lower third of the esophagus. Nd:YAG therapy is least successful in treating lesions of the cervical esophagus, in cancers more than 8 cm in length and in cancers that are primarily infiltrating or extraluminal (31). Only the intraluminal portion of the tumor can be treated. Treating tumors in the upper third of the esophagus is difficult with Nd:YAG therapy because it is hard to maneuver the fiber tip in this narrow region. Also, the patients are uncomfortable from the sensation of pressure and fullness in the throat caused by the insufflation of carbon dioxide; the trachea is immediately beneath the cervical esophagus. The patients become agitated and do not lay still, further complicating the delivery of Nd:YAG therapy. In lower-third lesions, angulation at the esophagogastric junction and technical

problems associated with movement in this area (such as heart palpitations, respiratory movements and peristalsis contractions) make Nd:YAG treatments difficult in this region. PDT is technically easier as it only requires the endoscopic placement of a fiber optic diffuser, prior to switching on the laser for the required treatment time and is less affected by patient motion. The improved objective response with PDT for tumors in the upper and lower third of the esophagus is clinically important, as one-half of esophageal carcinoma are located in these regions (2).

The advantage that PDT exhibits in treating small tumors is a reflection of PDT's ability to treat small flat tumors whereas Nd:YAG laser therapy is good at treating exophytic tumors. Because of the risk of perforation with the thermal ablation laser, the light beams must be aimed tangentially to the esophageal wall.

Similarly, a trend favoring PDT was seen in patients with prior therapy. Prior therapy for esophageal cancer, particularly radiation therapy, results in a flat, fibrotic tumor morphology, not easily treated with Nd YAG therapy. With Nd:YAG therapy, only the intraluminal portion of the tumor can be treated.

PDT with PHOTOFRIN should be judged on its own merit, not only in comparison to Nd:YAG therapy. To that end, a select subset of patients who responded very favourably to PDT with minimal adverse experiences was presented. Thirty-one patients were identified (20/110 from P19 and 11/17 from P20). Fourteen of these patients (45%) experienced adverse events of Grade-2 toxicity or less during the study. For the remaining 17 patients, only 5 patients (16%) experienced adverse events of Grade-3 or 4 toxicity that were considered treatment associated. Benefit was of clinically significant duration.

CONCLUSIONS

Two adequate and well-controlled studies of the safety and efficacy of PDT with PHOTOFRIN have been conducted for this indication. One study was a comparative study in which Nd:YAG laser thermal ablation was the control therapy. In the single-arm study, patients acted as their own controls, as no other safe therapy exists for these patients and spontaneous remissions do not occur in advanced esophageal cancer. The number of patients in the single-arm study, although small, is considered sufficient because of the definitive results obtained for these patients with no other acceptable treatment options.

PDT with PHOTOFRIN is an effective therapy for the reduction of obstruction and palliation of dysphagia in patients with partially or completely obstructing esophageal carcinoma. A single course of PDT therapy provides a significant improvement in dysphagia grade, objective response, and changes in luminal diameter. The comparative therapy, Nd:YAG laser, produced significant improvements as well, however, PDT was shown to be better at reducing the tumor obstruction. More treatment procedures were given with Nd:YAG therapy. Therefore, comparable or better efficacy was accomplished with PDT using fewer treatment procedures per patient."

8.0 Review of Integrated Summary of Safety

8.1 Overview of Studies in ISS

The applicant's Integrated Summary of Safety is located in Volumes 43 and 44 of the NDA. Supporting reports on individual studies are in volumes 45-54.
Table 1 describes the patients included in the sponsor's ISS. Primary studies, ie those closely monitored by the applicant, include 269 PDT patients treated in randomized studies, and 54 in noncomparative studies. The other 2 randomized studies are in lung cancer and bladder cancer. Supportive studies , including literature reports, include over 1800 patients. The sponsor had good quality data on 862 patients, and these are analzed in the ISS.

For the purposes of this NDA, the highest quality safety data for local PDT effects comes from the controlled study of PDT vs YAG in partially obstructing esophageal cancer. The highest quality data on systemic side effects would come from the randomized controlled trials which could include the bladder cancer and lung cancer trials. The large numbers of patients treated in various indications could be helpful for detecting severe and less frequent side effects.

The actual studies covered in the ISS are listed in the Applicant's table 2 (attached). Table 3 from the Summary , a descriptive table listing indication, design, dosing, # patients, and demographics of each of these studies is located on pp 24-33 of Volume 43. Attached are excerpts from this table describing the study design and the method of PDT administration for the major esophageal, lung, and bladder cancer studies.

Laser systems employed in the various studies were required to have the capability of providing up to 1 W of laser power from the distal end of that fiber optic diffuser and to maintain a wavelength of 630 +/- 3 nm during treatment.

Table 5 lists the 'primary studies' and shows extent of exposure, ie number of courses of PDT. 417 courses of PDT are included; 369 in a controlled setting. P19 and P20 are described in other parts of MOR #1 and MOR #2. P17 and P503 are studies of PDT versus Nd:YAG thermal ablation therapy in lung cancer. P18, P23, and P504 compare PDT plus radiation therapy (XRT) to XRT alone in lung cancer. The primary study in bladder cancer compared PDT to observation in as prophylactic therapy following TUR.

Extent of followup in primary studies is listed in the Applicant's table 6 attached. Median followup was very short in the esophageal studies (1.9 months), and longest in the study of papillary tumors (11.9 months).

TABLE 1. Number of Patients Summarized in the ISS

Indication	Clinical Pharm. Studies	Primary Studies			Supportive Studies[a]					Total[b]
		Comparative Studies		Noncomparative Studies	Comparative Studies		Investigator Protocols and Compassionate Use	Literature		
		PDT	Control	PDT	PDT	Control	PDT	PDT	Control	PDT
Esophageal Cancer	0	110	108	17	0	0	107	196	748	1,286
Lung Cancer								501	136	637
No XRT	12[c]	99	99	0	0	0	266	NA	NA	476
With XRT	0	35	33	0	29	26	0	NA	NA	123
Bladder Cancer								240	0	240
Papillary tumors	0	25	27	0	0	0	20	NA	NA	72
Carcinoma in situ (Tis)	0	0	0	37	6	7	0	NA	NA	50
Other Cancers	0	0	0	0	0	0	104	869	336	1,309
TOTAL	12	269	267	54	35	33	497	1,806	1,220	4,193

[a] Supportive studies quality of the studies is not sufficient either in conduct and/or documentation to be considered primary studies.
[b] Total number of PDT-treated patients, excluding those estimated in literature
[c] Five of these patients are also counted in primary comparative studies.
NA = Not applicable

TABLE 2. Overview of Studies Included in the ISS (Page 1 of 2)

Abbreviated Protocol Number	Oncologic Indication	Clinical Phase	Treatment Groups	Location	Enrollment Dates	Study Status
Primary Studies						
P19	Esophageal	III	PDT Nd:YAG	US + Canada, 24 centers	Sept. 1988 July 1992	Completed
P20	Esophageal	III	PDT	US + Canada, 8 centers	April 1989 August 1992	Completed
P17	Lung	III	PDT Nd:YAG	US + Canada, 20 centers	March 1989 April 1992	Closed early: slow accrual
P503	Lung	III	PDT Nd:YAG	9 European countries, 15 centers	April 1990 Nov. 1992	Completed
P18	Lung	III	PDT + XRT XRT	US, 18 centers	March 1989 Dec. 1991	Closed early: slow accrual
P23	Lung	III	PDT + XRT XRT	Canada, 2 centers	Dec. 1988 Oct. 1991	Closed early: slow accrual
P504	Lung	III	PDT + XRT XRT EBT + XRT	Netherlands, 1 center	April 1991- Dec. 1991	Closed early: slow accrual
P15	Bladder	III	PDT OBSERVATION	US 9 centers	Oct. 1988 Aug. 1991	Closed early: better than expected results with PDT
P32	Bladder	III	PDT OBSERVATION	US + Canada, 8 centers	April 1991 June 1992	Closed early: unacceptable toxicity
P24	Bladder	II	PDT	US + Canada, 15 centers	August 1989 - ongoing	Ongoing
P500	Bladder	II	PDT	6 European countries, 6 centers	March 1990 Sept. 1991	Closed early: Slow accrual

EBT = endobronchial brachytherapy
Nd:YAG = Neodymium:Yttrium-aluminum-garnet laser therapy
PDT = photodynamic therapy with PHOTOFRIN
XRT = X-ray therapy

TABLE 2. Overview of Studies Included in the ISS (Page 2 of 2)

Abbreviated Protocol Number	Oncologic Indication	Clinical Phase	Treatment Groups	Location	Enrollment Dates	Study Status
Supportive Studies						
PHO 999-1	Esophageal	NA	PDT	Canada, EDR, single center	Sept. 1988 August 1992	NA
P2	Lung	III	PDT+XRT XRT	US + Canada, 12 centers	Nov. 1985 July 1987	Closed early: change in sponsor
P21	Lung	II	PDT	US, 4 centers	April 1983 Nov. 1988	Completed
P6	Bladder	III	PDT Thiotepa	US + Canada, 4 centers		Closed early: change in sponsor
P10	Bladder	III	PDT BCG	US, single center		Closed early: change in sponsor
European Investigator Protocols/ Compassionate Use	9 assorted indications	II	PDT usually no control therapy	Europe, at least 12 centers	Up to April 1991	NA

EDR = Emergency Drug Release in Canada (compassionate use)
NA = not applicable
PDT = photodynamic therapy with PHOTOFRIN
XRT = X-ray therapy
BCG = bacillus Calmette-Guerin
= Data not available

TABLE 3. Summary of Primary Clinical Studies in the ISS

Abbrev. Protocol Number	Indication	Study Design	Dosing Schedule	Therapy: No. of Treated Patients	Demographics	NDA Location	
						Volume	Page
ESOPHAGEAL CANCER							
P19	Partially obstructing esophageal carcinoma	Open-label, randomized, controlled, multicenter PDT vs Nd:YAG	PDT PHOTOFRIN 2 mg/kg, after 40-50 hr, 630-nm APDL light, 300 J/cm of cylindrical fiber optic diffuser. Max 2 light treatments/course. Max. 3 courses. Nd:YAG 500-30,000 J/course; unlimited courses.	PDT: 110 Nd:YAG: 108	PDT Median Age (range) Gender 83 men 27 women		
LUNG CANCER							
P17	Obstructing or partially obstructing non-small cell bronchogenic carcinoma	Open-label, randomized, controlled multicenter PDT vs Nd:YAG	PDT PHOTOFRIN 2 mg/kg, after 40-50 hr, 630-nm APDL light; tumors <0.5 cm, 100 J/cm^2 via microlens fiber optic diffuser; tumors >0.5 cm, 200 J/cm of cylindrical fiber optic diffuser. Max. 2 light treatments/course. Max. 3 courses.	PDT: 33 Nd:YAG: 34	PDT Median Age (range) Gender 24 men 9 women	Appendix 5[b]	

TABLE 3. Summary of Primary Clinical Studies in the ISS

Abbrev. Protocol Number	Indication	Study Design	Dosing Schedule	Therapy: No. of Treated Patients	Demographics	NDA Location	
						Volume	Page
BLADDER CANCER							
Papillary Tumors							
P15	Prophylaxis for superficial papillary tumors following transurethral resection	Open-label, randomized, controlled, multicenter PDT vs OBSERVATION (OBS)	PDT PHOTOFRIN 2 mg/kg, after 40-50 hr, 630-nm APDL light via spherical fiber optic diffuser at 15 J/cm^2.	PDT: 20 OBS: 20	**PDT** **Median Age (range)** **Gender** 15 men 5 women	Appendix 13[b]	

TABLE 6. Extent of Follow-Up in Primary Studies

Indication	Number of Patients By Months of Follow-Up									
	PDT					Control				
	<3	3≤6	6≤9	9≤12	≥12	<3	3≤6	6≤9	9≤12	≥12
ESOPHAGEAL	86	30	9	1	1	72	24	10	2	0
LUNG CANCER										
no XRT	53	31	7	2	6	68	21	6	4	0
with XRT	12	9	3	5	6	12	9	7	2	3
BLADDER CANCER										
Papillary tumors	1	2	6	5	11	11	9	4	0	3
Tis	6	14	8	4	5	NA	NA	NA	NA	NA

	Median Months (Min.-Max.) of Follow-Up			
	PDT		Control	
ESOPHAGEAL CANCER	1.9	(0.1-12.7)	1.9	(0-11.6)
LUNG CANCER				
no XRT	2.5	(0.1-28.0)	2.0	(0-12.0)
with XRT	5.1	(0.2-25.2)	4.0	(0.7-28.2)
BLADDER CANCER				
Papillary tumors	11.9	(2.8-14.4)	3.3	(0-14.9)
Tis	5.7	(0.7-15.6)	NA	

NA = Not applicable

8.2 Deaths and Adverse Events

Safety results are summarized in the Applicant's table 10 for the primary studies, including adverse events by grade, withdrawals from study for adverse events, and deaths . Notable differences from this table aresummarized below (expressed in per cent of patients who had at least on AE):

From Esophageal studies:

Associated AE's	67% vs 37% YAG.
Moderate AE's	34% vs 15% YAG
Very Severe AE's	28% vs 15%YAG
Associated Deaths	6% vs 0% YAG (although 'independent assessor' founnd 5% on YAG).

From Lung studies

Associaed Aes	40% vs 23% and 86% vs 70%.
Associated deaths	6% vs 1% and 9% vs 3%

From Bladder study(controlled)

Severe AE's	72% vs 4% (no-treatment control)

TABLE 10. Safety Overview For All Indications

Number (%) of Patients

Variable	ESOPHAGEAL STUDIES[a] COMBINED				LUNG STUDIES[b] COMBINED						BLADDER STUDIES[c] COMBINED					
					no XRT				with XRT							
	PDT n=127		Nd:YAG n=108		PDT n=99		Nd:YAG n=99		PDT+XRT n=35		XRT n=33		Papillary Carcinoma PDT n=25		Papillary Carcinoma OBS n=27		Tis PDT n=37	
Patients With At Least 1 AE																		
All AEs	117	-92	88	-82	72	-73	63	-64	32	-91	30	-91	24	-96	7	-26	36	-97
Associated AEs	85	-67	40	-37	40	-40	23	-23	30	-86	23	-70	23	-92	0	0	36	-97
Most Severe AE																		
All AEs																		
Mild	9	-7	13	-12	11	-11	7	-7	7	-20	8	-24	2	-8	3	-11	1	-3
Moderate	37	-29	24	-22	20	-20	20	-20	6	-17	7	-21	4	-16	3	-11	7	-19
Severe	32	-25	33	-31	22	-22	25	-25	11	-31	9	-27	18	-72	1	-4	28	-76
Very severe	36	-28	16	-15	19	-19	8	-8	8	-23	6	-18	0	0	0	0	0	0
Associated AEs																		
Mild	18	-14	5	-5	11	-11	4	-4	12	-34	8	-24	1	-4	0	0	1	-3
Moderate	43	-34	16	-15	14	-14	13	-13	8	-23	8	-24	8	-32	0	0	8	-22
Severe	16	-13	13	-12	7	-7	5	-5	5	-14	3	-9	14	-56	0	0	27	-73
Very severe	8	-6	6	-6	8	-9	1	-1	5	-14	4	-12	0	0	0	0	0	0
Withdrawals Due to AEs																		
All AEs	16	-13	17	-16	3	-3	3	-3	0	0	0	0	0	0	0	0	4	-11
Associated AEs	8	-6	7	-6	3	-3	1	-1	0	0	0	0	0	0	0	0	3	-8

AE = Adverse event

[a] Esophageal studies: P19, P20

[b] Lung studies: no XRT P17, P503; with XRT P18, P23, P504

[c] Bladder studies: Papillary tumors P15, P32; Tis tumors P24, P500

TABLE 10. Safety Overview For All Indications

Variable	Number (%) of Patients											
	ESOPHAGEAL STUDIES[a] COMBINED				LUNG STUDIES[b] COMBINED						BLADDER STUDIES[c] COMBINED					
					no XRT				with XRT		Papillary Carcinoma				Tis	
	PDT n = 127		Nd:YAG n = 108		PDT n = 99		Nd:YAG n = 99		PDT + XRT n = 35		XRT n = 33		PDT n = 26		OBS n = 27		PDT n = 37	
Deaths Within 30 Days of Treatment Procedure																		
All Deaths	32	-25	23	-21	16	-16	17	-17	7	-20	3	-9	0	0	0	0	0	0
Associated Deaths	7	-6	0	0	6	-6	1	-1	3	-9	1	-3	0	0	0	0	0	0
Treating investigator	8	-6	5	-5														
Independent assessor																		
Deaths More Than 30 Days After Treatment Procedure																		
All Deaths	83	-65	70	-65	61	-62	59	-60	22	-63	22	-67	0	0	3	-10	2	-5
Associated Deaths	1	-1	0	0	0	0	1	-1	0	0	2	-6	0	0	0	0	0	0

[a] Esophageal studies: P19, P20
[b] Lung studies: no XRT P17, P503; with XRT P18, P23, P504
[c] Bladder studies: Papillary tumors P15, P32; Tis tumors P24, P500
= Data not available

323 patients were treated in primary studies of esophageal cancer, lung cancer, and bladder cancer. Most patients in the trials were (75% to82%) men, reflecting the demographics of these diseases. 13% of the patients on the PDT arm in the esopageal studies were black, whereas minorities composed less than 5% of the population for the other trials.

The sponsor notes that early deaths, overall survival, and withdrawals due to adverse events were similar on PDT and control therapies. Furthermore, the sponsor notes that bias might have increased the incidence of Associated AE reporting in these unblinded trials. Most toxicities were local: in esophageal studies there was edema, pain, pleural effusions, fever, and atrial fibrillation. In lung cancer, there was increased sputum, dyspnea, respiratory insufficiency, and fever. In bladder cancer there was increased urinary urgency and frequency, hematuria, pain, and genital edema.

The sponsor notes that adverse event rates were lower with the earlier frozen formulation.

The sponsor concludes the overview on P 68 of volume :

"Across all indications, no notable gender- or age-related differences in safety profile were observed. The safety of PDT with PHOTOFRIN was not evaluated in adolescents or children.

"In esophageal cancer studies, adverse events that occurred commonly (>10% of patients) in both the PDT and the control group were abdominal pain, nausea, dyspnea, pneumonia, anemia, chest pain, fever, and pain. Some of these adverse events reflect symptoms of esophageal cancer or concurrent conditions such as respiratory disease, although they may have been exacerbated by either treatment.

"Specific adverse events that occurred significantly more often in PDT-treated patients than in Nd:YAG-treated patients were photosensitivity reaction (19% versus 0%, respectively), fever (33% versus 10%), pleural effusion (28% versus 6%), respiratory insufficiency (10% versus 1%), anemia (26% versus 10%), and constipation (23% versus 9%). Esophageal perforation occurred significantly more often in Nd:YAG-treated patients (1% PDT, 7% Nd:YAG).

"With the exception of respiratory insufficiency and anemia, all of these were generally mild or moderate and easily managed. Anemia is manageable by transfusions, although this remains a quality-of-life issue for patients. Respiratory insufficiency is not easily managed and its etiology is unclear; only 3 of the 15 events were considered to be due to PDT. Esophageal perforation, the single adverse event that occurred at a statistically higher rate in the Nd:YAG group, is usually life-threatening and very difficult to manage."

Regarding deaths, in the summary of safety the Applicant describes the analysis performed by an independent assessor:

> "Within the P19 study, similar numbers of patients died within 30 days of a treatment procedure on both arms of the trial, 26 (24%) on PDT and 23 (21%) on Nd:YAG. None of the deaths in the Nd:YAG group were considered to be associated with treatment by the treating investigator, while 5 (5%) of the deaths in the PDT group were assessed as associated with the treatment. One death which occurred more than 30 days after a procedure was attributed to PDT treatment (Table 13).
>
> "A blinded review of all deaths occurring within 30 days was carried out by an independent assessor. Using the treatment association attributed by the independent assessor, 5% of patients in each treatment group died of treatment-associated causes."

A 'prominent gastroenterologist, and investigator on both studies' was given capsule summaries of all patients dying within 30 days of a procedure and asked to assess the association of the death to treatment. Summaries were blinded to treatment, investigator, and investigator-assigned association. The differences in assignment are shown in table 15 from the summary of safety:

TABLE 15. Association of Death to Treatment

Patient Number[a]	Treating Investigator	Independent Assessor
PDT		
	Possibly	Remote
	Remote	Possibly
	Definitely not	Possibly
	Definitely not	Possibly
	Possibly	Definitely not
	Definitely not	Possibly
Nd:YAG		
	Definitely not	Possibly
	Definitely not	Possibly
	Definitely not	Probably
	Definitely not	Probably
	Definitely not	Probably

[a] Capsule summaries provided in Appendix 2.3

The findings of the independent assessor added a net 2 more cases to PDT arm and 5 more to the YAG arm. All of the YAG differences were originally classified as 'definitely not' by the original investigator and then possibly or probably by the blinded assesor.

Reviewer comments:

I reviewed the patient summaries provided by the Applicant for the 5 YAG patients classified as treatment related deaths by the blinded assessor:

504	*bleeding/anemia*	*course2, day 32.*
251	*hematemesis*	*course 2, day 8*
648	*fistula/bronchitis*	*course 2 day 39*
2141	*perforation/CHF*	*day 25*
2043	*TE Fistula, PD,*	
	Aspiration pneumonia	*D21*

It is conceivable that all of these cases could be attributed to treatment. It is also conceivable that investigators might be more willing to assign blame to a new treatment in an unblinded trial. However, neither of these analyses sufficiently give criteria for attribution. I have my doubts whether an experienced investigator could truly be blind to a history which would be revealing enough to allow causality to be determined.

I do think the Applicant has cast some doubt on this finding, but I still find it significant that the investigators attributed an excess of treatment-related deaths to PDT.

The sponsor analyzed deaths within 30 days of a photofrin injection and presented the findings in table 16:

TABLE 16. Summary of Causes of Death Within 30 Days of a Procedure For PDT-Treated Patients by PHOTOFRIN Formulation in Esophageal Cancer Studies

Cause of Death	Number (%) of Patients							
	Frozen (n = 47)				Lyophilized (n = 88)[a]			
	All		Associated[b]		All		Associated[b]	
Progressive Disease	6	(13)	1	(2)	12	(14)	2	(2)
Cardiovascular								
Myocardia infarction/cardiac arrest	0	(0)	0	(0)	3	(3)	0	(0)
Congestive heart failure	0	(0)	0	(0)	2	(2)	1	(1)
Cerebrovascular accident/brainstem infarct	0	(0)	0	(0)	1	(1)	0	(0)
Respiratory								
Pneumonia	0	(0)	0	(0)	2	(2)	1	(1)
Pulmonary hemorrhage	0	(0)	0	(0)	1	(1)	0	(0)
Gastrointestinal								
Gastrointestinal tract hemorrhage	0	(0)	0	(0)	2	(2)	1	(1)
Infection	1	(2)	1	(2)	1	(1)	1	(1)
Other								
Lung cancer	0	(0)	0	(0)	1	(1)	0	(0)
Unknown	1	(2)	0	(0)	0	(0)	0	(0)
TOTAL DEATHS	8	(17)	2	(4)	24[c]	(27)	5[c]	(7)

[a] A total of 127 patients received PDT. Eight patients were switched from frozen to lyophilized PHOTOFRIN formulation at the second or third course. None were early deaths.
[b] As assessed by the treating investigator
[c] Patient had progressive disease/aspiration pneumonia listed as causes of death. This patient is listed twice in the table but not in the total.

Incidence of death within 30 days of a procedure was 17% with fronzen formulatoin versus 27% with lyophilized formulation. The additional 10% in the lyophilized arm consisted of cardiovascular, respiratory, and GI events. the sponsor states that early deaths occurred in 21% of YAG patients concurrent to patients receiving lyophilized Photofrin.

Adverse Events

In this section the Applicant reviews data which were reviewed in the individual study reports. See the Medical Review of these reports for details.

8.1.1 Formulation issue:

On pp 124-127 of volume 43 the Applicant gives a table comparing frequencies of adverse events by individual category versus formulation (Frozen versus Lyophilized). The following is the applicant's conclusion after review of this table:

"The pattern of adverse event reporting was similar for the two formulations, with some differences noted in specific events. The following comparisons are based on data from Study P19. More patients receiving the lyophilized formulation (96%) reported adverse events than patients receiving the frozen formulation (81%). Although only anemia occurred at a statistically higher rate with the lyophilized formulation (34% versus 9%), the trend towards higher rates with the lyophilized formulation was consistent for many adverse events that may be due to PDT. Nausea, abdominal pain, vomiting, esophageal edema, pleural effusions, confusion, anorexia, back pain, weight decrease, and atrial fibrillation occurred more often with the lyophilized formulation, although not statistically different.

Notably, reporting rates for respiratory insufficiency, fever, chest pain, and photosensitivity reaction were unaffected by formulation. One event, tracheoesophageal fistula, was more common in patients receiving frozen drug (16%) than in patients receiving lyophilized drug (4%) or Nd:YAG therapy (7%)."

8.3 Applicant's review of selected Adverse Events

(Detailed tables on each point are located on pp 181-218 of volume 43)
The sponsor has separately reviewed selected adverse events in the esophageal studies. The following are reviewer notations upon reviewing the text and tables from this section:

Applicant's review of Tracheo-esophageal Fistulas

- In study P19, the incidence is 9% on PDT vs 8% on YAG.
- Death within 10 days occurs with an incidence of about 10% on each arm.
- TEF occurs more frequently in lesions in the upper 1/3 of the esophagus.
- Events occur earlier in time on YAG arm (median of 7 days vs 27 days).

Applicant's review of Esophageal perforations:

- WHO coding for perforation is 'esophageal ulceration'
- Incidence was higher on PDT arm in P19 (1% vs 6%).
- 4 of 6 perforations on the YAG arm occurred in the first 10 days.
- Only 1 of 6 YAG perforations led to death within 20 days. 4 of 6 lived more than 30 days.

Reviewer comments:

In numerous places in the NDA the reader is reminded about the seriousness of this side-effect, which is seen predominently in the P19 study, on the YAG arm. Therefore, the finding that 4 of 6 patients lived more than 30 days is surprising and suggests that this diagnosis does not always lead to immediate demise.

Applicant's review of Anemia

- Incidence in P19 was 26% on PDT vs 12% on YAG..
- Anemia was more common with large tumors and distal tumors.
- In the PDT arm, 13%, 33%, and 47% respectively developed anemia before 4 days, 4-10 days, and >10 days respectively after laser.

Applicant's review of Fever

- Incidence was 32% PDT vs 10% YAG.
- Incidence was 37% with Frozen formulation vs 26% with lyophilized.
- Occurred more often in women (on PDT arm incidence 48% vs 27%).
- about half of the cases were of unknown origen.

Applicant's review of Pleural effusions

- Incidence 27% on PDT vs 6% on YAG.
- 63% of such events on PDT arm did not require treatment.
- only one case on PDT arm required thoracentesis.
- 44% occurred within 3 d, 75% within 10 d of laser treatment.

Applicant's review of Atrial Fibrillation

- Incidence was 8% on PDT arm vs 4% on YAG arm of study P19.
- Incidence was 11% with lyophilized formulation vs 2% with frozen.
- Event was more frequent with middle esophageal lesions (16% on PDT)
- The 4 cases of severe or life-threatening events were on PDT arm of P19.
- On PDT arm, 25% of the events occurred within 3 days, 67% within 10 days of treatment.
- Duration of A. Fibrillation was < 48 hours in 50% on the PDT arm.

Applicant's review of Respiratory Insufficiency

- This occurred in 11% on PDT arm vs 1% on YAG arm of P19.
- In P20 (completely obstructed disease) the incidence was 18%.
- 9 of the 10 cases occurred in the first course on the PDT arm.
- This occurred both with the lyophilized (8%) and frozen (12%) formulations.
- As with A. Fibrillation, this is more common with mid-esophageal lesions (17%).
- Incidence could not be predicted on basis of pulmonary history or findings.
- In PDT arm, 17% (2 cases) occurred within 3 days, and 42% within 10 days of treatment.
- Death occurred within 3 days of event in 45% of cases.

Reviewer comments:

In comparison to esophageal perforation, this event appears to have been more an immediately life-threatening adverse event.

In reading through the clinical capsules of individual patients with this adverse event, no consistent pattern emerges. Many deaths were associated with aspiration, infection, or hemoptysis similar to problems one might encounter in untreated patients with this disease.

Applicant's review of Cerebrovascular Accidents

- Incidence was 6% on YAG versus 1% on PDT in P19 study.
- 5 of 6 were considered severe or life-threatening on the YAG arm.
- 2 of 6 of the events on the YAG arm occurred within 3 days, the other 4 occurred later than 10 days after laser treatment.
- Death occurred more than 10 days after the event in 5 of 6 patients.

Applicant's review of Constipation

- Constipation occurred in 22% on PDT vs 9% on YAG in P19.
- It was more common with the lyophilized formulation (23% vs 16%)
- It was more common in the elderly (26% vs 8% for age over vs under 60 years).
- Its incidence was highest in patients taking narcotic analgesics (50%).

Applicant's review of Ocular abnormalities

These events occurred in 5 patients, all on the PDT arm of P19 (1-107, 4-566, 8-659, 8-1441, 16-801). Abstracts of these patients are located on p 229-230 of Volume 43 of the NDA.

- 1-107 Pt. had *mild ocular sensitivity* lasting 16 days associated with photosensitivity of skin of face.
- 4-566 Pt. had severe *optic neuritis and narrow angle glaucoma.* She had fever on the 3rd day (laser day) of the second course and started cephalosporins on day 4. On that day severe blurred vision and pain led to a diagnosis of optic neuritis, followed by narrow angle glaucoma on day 13.
- 16-801 This patient complained of decrease in visual acuity at a distance on Day 76 which persisted and was considered not associated with treatment.
- 8-659 Pt. had 'severe blurry vision' on day 36 judged not treatment associated. He had metastases to orbit and brain.
- 8-1441 On day 6 of course 2 Pt. had a 30 minute episode of diploplia. This was not considered by investigator to be related to therapy.

Reviewer comments:

Only patients had events which clearly seem related to pdt one occurring in conjuction with laser light treatment and one obviously associated with sun exposure.

8.4 Applicant's Summary from Esophageal Cancer section of NDA 'Summary of Safety'

The Applicant's 5-page summary from the Summary of Safety is reproduced in its entirety. The last paragraph contains the Applicant's conclusions:

"Summary of Safety Profile in Esophageal Cancer

The safety profile of photodynamic therapy (PDT) with PHOTOFRIN for the treatment of esophageal cancer is based on data from 127 patients, 110 with partially obstructing esophageal tumors and 17 with completely obstructing tumors. For comparison, safety data will be discussed for 108 patients with partial obstructions who were treated with thermal ablation therapy using the Neodymium:Yttrium-aluminum-garnet (Nd:YAG) laser. These patients were treated in two clinical studies, Study P19, an open-label, randomized, comparative trial in patients with partially obstructing tumors, and Study P20, a single-arm trial in patients with completely obstructing tumors.

Patient characteristics were similar between groups in the randomized trial. Minor differences are not expected to affect the comparison of safety profiles between the two therapies. The majority of the patients were Caucasian (87%), men (71%), 60 years of age or older (83%), with a median Karnofsky Performance Status (KPS) of 80 and a median dysphagia grade of 3 (unable to swallow any solids, able to swallow liquids without any difficulty). Approximately half of the patients had received prior therapy for esophageal cancer; one-quarter of the patients had received multiple therapies for esophageal cancer. In the single-arm study (P20), equal proportions of patients were men or women and the median dysphagia grade was 5 (unable to swallow anything, including saliva) due to complete obstruction of the esophagus. Complete obstruction was defined as the inability to pass a guide wire past the tumor.

Regarding the most important safety endpoints (early death rate, overall survival, and rate of withdrawal due to adverse events), the two therapies were the same. Median survival was 4.0-4.6 months in the comparative trial; 21-24% of patients died within 30 days of a procedure, most of progressive disease; 12-16% of patients were withdrawn from study due to adverse events, usually the development of a tracheoesophageal fistula. Five early deaths in PDT-treated patients and none in Nd:YAG-treated patients were assessed as treatment associated by the treating investigator. Because this was an open-label trial in which the comparative therapy was a surgical technique, it was recognized that a bias may have existed due to the investigators' reluctance to attribute an early death to their own abilities as a surgeon. Therefore, a blinded evaluation of

possible treatment association for all early deaths was obtained from an independent assessor. According to this blinded assessment, early deaths were associated with treatment for six PDT-treated patients and five Nd:YAG-treated patients.

In Study P20, the median survival was shorter at 2.8 months, reflecting the more advanced condition of these patients with total obstruction. Thirty-five percent of patients died within 30 days of a procedure and 18% were withdrawn due to adverse events.

In general the PDT adverse event profiles observed in the two studies were similar. Therefore, the following discussion will focus on the data from Study P19, with mention of notable exceptions in Study P20.

Most patients in each treatment group experienced adverse events (PDT, 92% of patients; Nd:YAG, 82%). Considerably more patients in the PDT group experienced adverse events that were considered to be treatment associated (66% PDT, 37% Nd:YAG). With respect to severity, the combined frequency of severe or very severe (life-threatening) adverse events was comparable for the two groups (52% PDT, 45% Nd:YAG), but a higher proportion of PDT-treated patients experienced adverse events that were very severe (29% PDT, 15% Nd:YAG). This difference was due primarily to a 10% incidence of respiratory insufficiency in PDT-treated patients versus a 1% incidence in Nd:YAG-treated patients. In both groups, 6% of patients experienced very severe adverse events that were considered to be treatment associated.

Adverse events related to the gastrointestinal, respiratory, and body-as-a-whole body systems occurred in approximately two thirds of PDT-treated patients and one-half of Nd:YAG-treated patients. Adverse events that occurred in more than 10% of patients in either group were abdominal pain, nausea, dyspnea, pneumonia, anemia, chest pain, fever, pain. Many of these adverse events reflect symptoms of esophageal cancer or concurrent conditions such as respiratory disease, although they may have been exacerbated by either treatment.

Specific adverse events that occurred significantly more often in PDT-treated patients were photosensitivity reaction, fever, pleural effusion, respiratory insufficiency, anemia, and constipation. Esophageal perforation occurred significantly more often in Nd:YAG-treated patients.

All patients who receive PHOTOFRIN will be photosensitive. Photosensitivity reaction occurred in 19% of PDT-treated patients. The majority of the episodes were mild in severity (78%) and required no treatment (75%). No patient was

withdrawn from study due to a photosensitivity reaction. The extent of this adverse event is a reflection of patient education and the willingness of the patients to comply with precautions.

Fever occurred in 33% of PDT-treated patients and 10% of Nd:YAG-treated patients. In Nd:YAG-treated patients, fever was usually linked to an infection, whereas in PDT-treated patients, fever was also linked to a possible inflammatory response in the treated area. Causality could not be determined for approximately half of the fevers in both groups. Almost all of the fevers were mild or moderate.

Pleural effusions occurred in 28% of PDT-treated patients and 6% of Nd:YAG-treated patients. The majority (84%) of episodes in PDT-treated patients were mild or moderate and two-thirds required no treatment. One Nd:YAG-treated patient was withdrawn from study due to pleural effusions; no PDT-treated patients were withdrawn for this reason.

Respiratory insufficiency occurred more frequently in the PDT group than in the Nd:YAG group (10% versus 1%, respectively). The majority of episodes occurred more than 10 days after laser light application. No prognostic factors were identified. Only 3 of the 15 episodes of respiratory insufficiency in PDT-treated patients were considered to be treatment associated.

Anemia was recorded as an adverse event for more PDT-treated patients (26%) than Nd:YAG-treated patients (12%). Blood transfusions were given to more PDT-treated patients (23% PDT, 15% Nd:YAG). More patients in the PDT group were anemic at baseline (25% versus 17%). Moreover, based on hemoglobin data, comparable proportions of patients in each group with normal baseline values demonstrated anemia while on study (33% PDT, 30% Nd:YAG). One patient in the PDT group was withdrawn from study because of anemia, which was not considered to be treatment associated. Anemia was not due to myelosuppression, but rather due to tumor bleeding and chronic illness. The Nd:YAG laser has an advantage in this regard, because it coagulates and cauterizes during thermal ablation of the tumor. Tumor killing is slower with PDT, requiring a few days for maximum necrosis to occur. During this time, the tumor may continue to bleed. A higher incidence of anemia was noted in PDT-treated patients with tumors longer than 10 cm and in those with tumors located in the lower third of the esophagus, the most vascular region.

Constipation occurred at twice the rate in the PDT group (23% PDT, 9% Nd:YAG) and this difference could not be explained by use of concurrent medications. Almost all occurrences were mild or moderate and easily managed.

Esophageal perforation is a very serious and usually life-threatening event due to the potential for the development of mediastinitis and massive infection. Perforations occurred more frequently with Nd:YAG treatment (1% PDT, 7% Nd:YAG). One PDT-treated patient was withdrawn from study due to perforation of the esophagus, not considered to be treatment associated. Three Nd:YAG-treated patients were withdrawn due to perforations and all three events were assessed as associated with treatment. The perforation rate in Study P20 was 18%, reflecting the difficulty in treating patients with complete obstruction. Perforations are acute events, occurring during laser ablation therapy or associated with instrumentation such as dilatation or debridement. Perforations are to be distinguished from tracheoesophageal fistulas (TEFs), which typically occur later, sometimes linked with instrumentation, but often due to the resolution of tumor that has invaded the neighboring trachea or due to disease progression. TEFs occur spontaneously in about 15% of patients in the natural course of the disease (17). The TEF rate seen in this study (9%) was the same for both treatment groups.

Cerebrovascular accidents (strokes) occurred at a higher rate in Nd:YAG-treated patients (1% PDT, 6% Nd:YAG). While most strokes occurred 2 or more weeks after laser treatment, two events occurred in Nd:YAG-treated patients within 2 days of the laser session. The mechanism by which the strokes occurred in these patients is unknown. One PDT-treated patient and two Nd:YAG-treated patients were withdrawn from study due to strokes and one patient in each group died from a stroke, none of which were considered to be associated with treatment.

Upon review of adverse events for individual patients, particularly those temporally associated with therapy, a pattern emerges that is one of an inflammatory reaction resulting from the photodynamic process, occurring primarily in the immediate area that received laser light, but occasionally extending into some adjacent tissues. The specific adverse events that suggest an inflammatory reaction are esophageal edema, chest pain, fever, pleural effusions, and atrial fibrillation. Some inflammation occurred in patients treated with Nd:YAG but to a lesser extent than occurred in PDT-treated patients.

Chest pain was reported as frequently in both treatment groups (19-23%). Esophageal edema (6% PDT, 2% Nd:YAG) and atrial fibrillation (8% PDT, 4% Nd:YAG) occurred more frequently in PDT-treated patients, although the number of events was small and the differences were not statistically significant. Esophageal edema occurred within 10 days of a laser light application, in patients with tumors located in the upper third of the esophagus. Atrial fibrillation occurred more often in PDT-treated patients with tumors located in the middle third of the

esophagus. Anatomically, the middle third of the esophagus passes directly behind the left atrium of the heart.

Adverse events were analyzed by patient gender and age. Gender- and age-related differences were few. Nausea, vomiting, and fever rates were higher in women in both treatment groups. Hematemesis occurred more often in patients <60 years in both groups. TEFs and respiratory insufficiency occurred more frequently in younger PDT-treated patients.

Approximately halfway through the randomized trial, the formulation of PHOTOFRIN was changed from a frozen solution (F) to a lyophilized product (L). The frozen solution was not convenient to use as it required storage at -20°C. Analysis of adverse event rates by PHOTOFRIN formulation revealed a greater incidence of specific events in patients who received the lyophilized formulation. Although only anemia occurred at a statistically higher rate with the lyophilized formulation, the trend towards higher rates with the lyophilized formulation was consistent for many of the adverse events that may be due to PDT. Notably, reporting rates for respiratory insufficiency, fever, chest pain, and photosensitivity reactions were unaffected by formulation. Statistical testing in this setting is not definitive because patients were not randomized to the two formulations.

Rates of early death and withdrawal due to adverse events were not statistically different for the two formulations. A shift to greater severity of adverse events was seen with the lyophilized formulation. The incidence of very severe adverse events was the same for both formulations (30% F, 25% L), but severe events occurred more often following treatment with the lyophilized formulation (9% F, 28% L).

Using the entire safety database for patients treated with either formulation provides an acceptable estimate of the safety profile of PDT. This is true because when the data collected using the lyophilized formulation were compared with the appropriate concurrent Nd:YAG data, the differences between therapies were essentially the same as discussed above based on the entire database, although the percentages were changed slightly. The only additional differences noted between therapies were that with PDT therapy, abdominal pain, nausea, and vomiting occurred at twice the rate seen following Nd:YAG therapy, confusion occurred at a statistically higher rate, and respiratory insufficiency was no longer statistically different.

In summary, the primary safety endpoints of early death and withdrawals due to adverse events showed PDT and Nd:YAG therapies to be comparable. Patients treated with PDT with PHOTOFRIN experienced more adverse events in general

than patients treated with Nd:YAG laser therapy, although one must recognize the potential for bias in the open-label setting, particularly when the comparative therapy is a surgical technique. PDT therapy, by its mechanism of action, induces an inflammatory reaction in the immediate treated area that sometimes spreads to adjacent tissues. The toxicities resulting from therapy are manifestations of this inflammatory response and the time required for necrosis of tumor to be complete. The only systemically induced effects of PDT with PHOTOFRIN appear to be photosensitivity and constipation. The adverse events that occurred at statistically higher rates with PDT were photosensitivity reaction, fever, pleural effusion, respiratory insufficiency, anemia, and constipation. With the exception of respiratory insufficiency and anemia, all of these were generally mild or moderate and easily managed. Anemia is manageable by transfusions, although this remains a quality-of-life issue for patients. Respiratory insufficiency is not easily managed and its etiology is unclear; only 3 of the 15 events were considered to be due to PDT. Esophageal perforation, the single adverse event that occurred at a statistically higher rate in the Nd:YAG group, is usually life-threatening and very difficult to manage."

8.5 Other Indications:

The sponsor's summary of safety for studies and other indications (volume 44) will be reviewed in Medical Officer Review #3.

8.6 Applicant's conclusions from Summary of Safety

The following are the Applicant's conclusions from the summary of Safety from page 300 of volume 44 of the NDA:

"• For all indications (esophageal,), PDT with PHOTOFRIN is comparable to control therapies, with respect to the rate of early death (within 30 days of a procedure), overall survival, and withdrawals from therapy due to adverse events.

• Adverse event reporting rates are generally higher and sometimes of slightly greater severity in PDT-treated patients, but the differences are not always statistically different from rates in patients treated with control regimens. All of the studies conducted were open label and the possibility of bias against a new therapy with unknown effects is recognized.

- The toxicities associated with PDT are primarily local, in the immediate area that receives laser light, and sometimes extending into adjacent tissues. The local/regional reactions are consistent with an inflammatory reaction induced by the photodynamic effect.

- In patients with esophageal cancer, this inflammatory reaction may cause esophageal edema, pain, pleural effusions, fever, and occasionally atrial fibrillation.

- Anemia, due to tumor bleeding and chronic illness, occurs in approximately 30% of esophageal cancer patients treated with PDT using PHOTOFRIN. Patients with large tumors (> 10 cm) and those with tumors located in the lower third of the esophagus, the most vascular region, are at greater risk of developing anemia.

- PDT with PHOTOFRIN is equally tolerated by men and women and by elderly patients. The safety of this therapy in adolescents or children has not been evaluated.

- Photosensitivity reaction and constipation are the only systemically induced effects of PDT with PHOTOFRIN, occurring in 20% and 15% of patients, respectively."

9.0 Applicant's Overall Conclusions on Benefits and Risks

The following conclusions are from the applicant's Integrated Summary of Benefits and Risks:

"CONCLUSIONS

Two adequate and well-controlled studies of the safety and efficacy of PDT with PHOTOFRIN have been conducted for this indication. One study was a comparative study in which Nd:YAG was the control therapy. In the single-arm study, patients acted as their own controls, as no other safe therapy exists for these patients and spontaneous remissions do not occur in advanced esophageal cancer. The number of patients in the single-arm study, although small, is considered sufficient because of the definitive results obtained for these patients with no other acceptable treatment options.

PDT with PHOTOFRIN is an effective therapy for the reduction of obstruction and palliation of dysphagia in patients with partially or completely obstructing esophageal carcinoma. A single course of PDT provides a significant improvement in dysphagia grade, objective response, and changes in luminal diameter. The comparative therapy, Nd:YAG laser, produced significant improvements as well; however, PDT was shown to be better at reducing the tumor obstruction. More treatment procedures were given with Nd:YAG therapy. Therefore, comparable or better efficacy was accomplished with PDT using fewer treatment procedures per patient.

PDT does not adversely affect survival compared to Nd:YAG therapy. The morbidity associated with PDT therapy is notable, but most of the effects are easily managed. The two adverse events of greatest concern are anemia and respiratory insufficiency. It is clear that PDT increases the risk of anemia, due to increased tumor bleeding, particularly in large tumors and in those in the lower third of the esophagus, which is the most vascular region. It is not clear that respiratory insufficiency is linked to PDT. Being able to swallow is such an important quality of life issue for these very ill and terminal patients, that the risk of possible adverse events, even at the rates observed in these studies, is justified.

Nd:YAG therapy also has associated morbidity, which is generally less than that seen with PDT therapy. However, esophageal perforation, the single adverse event that occurred at a statistically higher rate in the Nd:YAG group, is usually life-threatening and very difficult to manage.

In patients with total obstruction, the improvements in dysphagia grade are dramatic. These patients cannot swallow their own saliva before therapy and are at risk of developing aspiration pneumonia. Therefore, PDT with PHOTOFRIN provides therapy with a remarkable benefit/risk ratio for these patients who have no other acceptable palliative options.

It is notable that 18% of PDT-treated patients with partial obstructions and 65% of patients with complete obstructions achieved very favorable efficacy with minimal or no toxicity, and therefore demonstrated a very good benefit/risk ratio with this therapy."

10.0 Reviewer Conclusions on Benefits and Risks

The main subject of Medical Review #1 was review of the data and the study report of Study P19 (Randomized controlled study in partially obstructed esophageal cancer, P19). The current review covers Study P20 (17 patients with completely obstructing esophageal cancer) and the Sponsor's summaries of Safety and Efficacy (see appendix I of this review or the material prepared for ODAC by the applicant).

In the integrated reviews of safety and efficacy, the sponsor, in addition to summarizing and integrating data, performs some new analyses of individual patient data, such as the graphical presentation of safety and efficacy information on patients selected by the sponsor. These analyses supplement the information noted in review of the study reports of P19 and P20.

The following points were noted by the reviewer upon review of the sponsor's summary of safety:

- The randomized study shows convincing statistically significant differences between PDT and YAG arms in toxicity. The sponsor argues that some of the difference may be due to bias of unblinded investigators and that many of the toxicities are not terribly significant.

- Patient profiles suggest net patient benefit in several patients with completely obstructing disease. It will be important to consider whether there are really no other options for these patients with the perforation rate of 18%.

- The sponsor has emphasized the seriousness of perforation as a side-effect of PDT. However, it was surprising that 4 of 6 PDT patients with perforation survived more than 30 days after the event.

- The sponsor had a blinded reviewer assess the attribution of causality to early deaths and found no significant difference between YAG and PDT arms. I agree that bias could be a problem with investigator judgments in these trials. However, I am not sure about the legitimacy of selective re-review of judgments based on an initially adverse analysis. If such initial findings had been in favor of the treatment arm, one wonders whether such a re-analysis would ever have been done. There is a question whether any reviewer of the clinical data could be blinded to arm, given the nature of the two treatments. In addition, the blinded reviewer had access only to patient 'capsules,' whereas the investigators were familiar with the entire patient course. I am left with uncertainty regarding this finding but cannot disregard it.

- In the sponsor's analysis of the formulation issue, it is noted that, when compared with data from patients randomized to the YAG arm concurrent to administration of lyophilized Photofrin, conclusions are similar, whether data is used from patients on the PDT arm who received frozen or who received lyophilized formulations. The question still exists, however, why did the adverse events seem to increase on PDT arm with the lyophilized formulation.. In

Medical Review #1, an increased rate of adverse events was noted on PDT over time and a decreased rate of events was noted on YAG over a similar period of time. The sponsor did not present any analysis which compared YAG AEs in patients randomized before and after the formulation amendment in January 1990.

- The sponsors notation that of all pleural effusions on the PDT arm, only one required thoracentesis suggests that this was not a major clinical problem.

- The PDT arm of study P19 had 4 cases of severe or life-threatening atrial fibrillation.

- In study P19, respiratory insufficiency was a significant problem on the PDT arm (11% vs 1%) with serious consequences (death within 3 days in 45% of pts). GAW 9-13-97

- Cerebrovascular events were more common on the ~~PDT~~ YAG arm (6% vs 1%).

- There were 2 convincing cases of ocular abnormalities on the PDT arm.

- Photosensitivity reactions were, for the most part, mild. The effect of having to avoid sunlight on quality of life is a point to consider.

- Treatment related adverse reactions were much more frequent on the PDT arm. The sponsor notes that some of this difference could have been from bias due to the open (non-blinded) nature of the trial. This is difficult to assess, but is a common problem in oncology trials.

GAW - 9-3-97

There are many reasons why one cannot claim that efficacy with PDT is equivalent to efficacy with ~~Photofrin~~ YAG. For instance, it is not clear to me which, if any, of the efficacy endpoints analyzed are know to be sufficient endpoints to encompass the efficacy of YAG therapy of esophageal cancer. An endpoint used to prove equivalence in efficacy should be sufficient to encompass the primary benefit produced by the control treatment. Even if the endpoints were adequate, the quality of data was not adequate to allow a valid statistical comparison between arms: dropout or lack of compliance due to the severity of the illness led to incomplete followup efficacy data. For this reason, though study P19 was able to demonstrate a difference in toxicity information between arms, the finding of no significant difference in efficacy has relatively little meaning. If one did not have a difference in toxicity between arms, then analysis of efficacy of each patient compared to his baseline might be sufficient to allow approval. This would be based on efficacy compared to a patient's own baseline and toxicity which is no worse than the control. The real issue for the indication of partially obstructing disease is how significant, how 'real' and how clinically relevant, is the difference in toxicity between the PDT and YAG arms. If it is determined to be clinically relevant, then I would not favor approval for this indication: we have proof of excess toxicity with no satisfactory comparison of efficacy for reasons given above. The assistance of the Advisory Committee in assessing the clinical relevance of the findings in P19 will be appreciated.

For the indication of completely obstructing disease, I think the sponsor makes a reasonable argument that several patients had significant clinical benefit. However, there was an 18% perforation rate in this study. The Advisory Committee will also assist the Agency with assessing the balance of benefit, as demonstrated in individual patient graphical display of efficacy data, to overall toxicity. Toxicity information can be gleaned from the graphical displays of individual patients, from data from the P20 trial(completely obstructing disease) and from comparative analyses in Study P19 (partially-obstructed disease.)

Regulatory Recommendations

1. The advice of the Oncologic Drugs Advisory Committee should be sought regarding the risk/benefit ratio of PDT in complete and in partially obstructing esophageal cancer.

2. The sponsor should perform analyses of efficacy and toxicity according to manufacturing scheme of Photofrin produced in P19 and P20 trials. The Medical Officer's preliminary analyses should be sent to the sponsor by FAX transmissions.

9-9-94

Grant Williams, MD

9/13/94

CC:
Richard Felten CDRH HFZ-410
HFD 340 Gurston Turner
HFD 150 Division Files, Gwilliams, Pzimmerman(2)
O.rig NDA 20-451
~~Document File~~

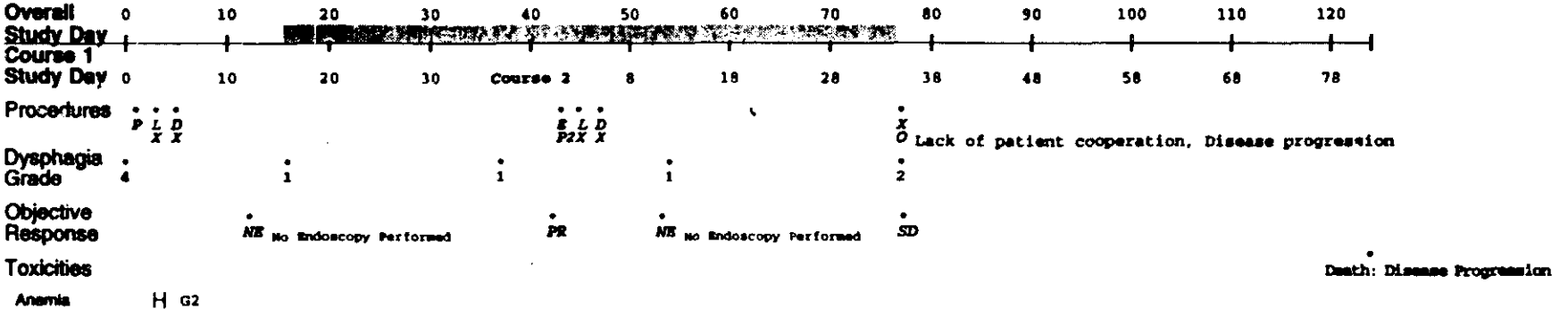
Appendix I

Applicant Graphical Presentation of Esophageal Cancer Patients Rx with PDT and with favorable benefit-Risk Ratio, examples.

Figure 1: Graphic Presentation of Efficacy and Safety for Patient

Age: 80
Gender: Male
Histology: Squamous Cell Carcinoma
Tumor Length: 8 cm

Tumor Location: Middle Third
Submucosal Involvement: Unknown
Prior Therapy: No
PHOTOFRIN Formulation: Lyophilized



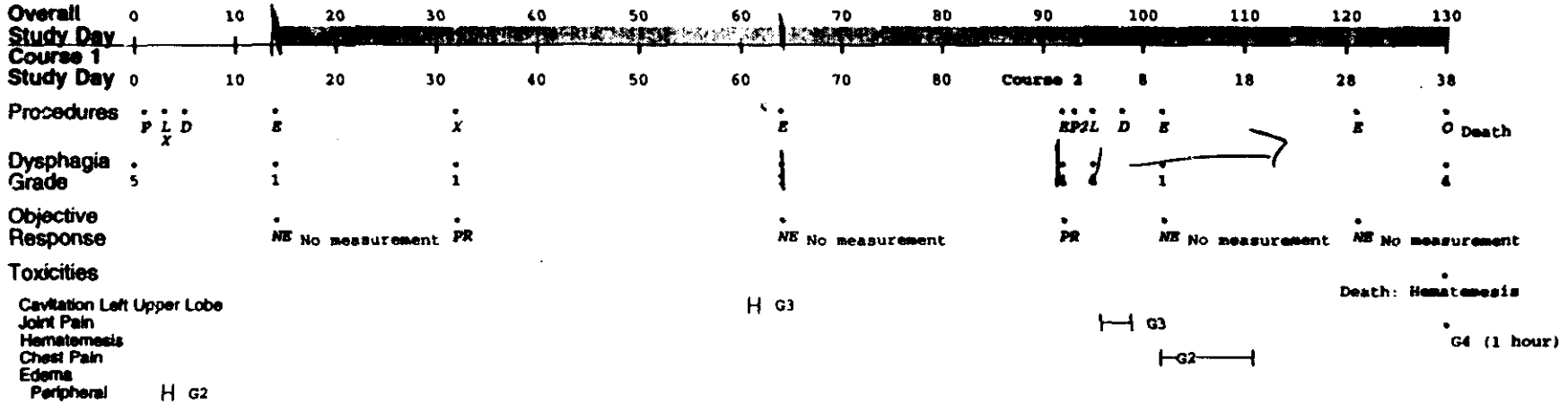
Patient was enrolled into Study P19 with an 8-cm tumor and dysphagia of Grade 4. The patient had metastatic disease involving the liver. At the Week-1 assessment, dysphagia had improved to Grade 1. The objective response was not evaluable as the esophageal lumen was not measured. At the Month-1 visit, the dysphagia grade remained improved, and a partial objective response was assessed. The investigator decided to give a second course of therapy, which resulted in further maintenance of the improved dysphagia (Grade 1). One month after the start of Course 2, dysphagia had worsened to Grade 2, but the objective response was assessed as stable disease. The patient was taken off study by the investigator at this visit. He subsequently died 6 weeks later of disease progression. The patient experienced a three-grade improvement in dysphagia with no concurrent toxicities of Grade 3 or greater.

Legend: CR Complete Remission D Debridement E Endoscopy L Laser Light Application LTF Lost to Follow-up NE Not Evaluable O Off Study PD Progressive Disease P PHOTOFRIN Injection PR Partial Remission SD Stable Disease X Endoscopy & Dilatation

Figure 3: Graphic Presentation of Efficacy and Safety for Patient

Age: 79
Gender: Male
Histology: Squamous Cell Carcinoma
Tumor Length: 4 cm

Tumor Location: Lower Third
Submucosal Involvement: Yes
Prior Therapy: No
PHOTOFRIN Formulation: Frozen



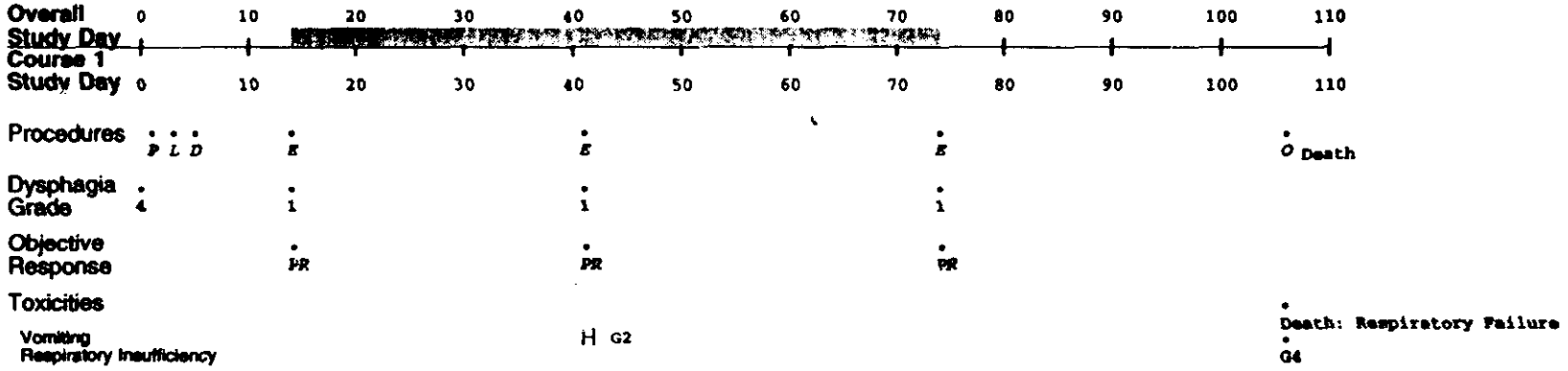
Patient was enrolled into the study with a 4-cm tumor located in the lower third of the esophagus. Following PDT, he achieved a reduction in baseline dysphagia from Grade 5 to Grade 1, which lasted about 2 months. A partial objective response was recorded at the Month-1 assessment but the Month-2 assessment was not evaluable. A cavitation (Grade 3) was observed in the left upper lobe of the lung 2 months after being treated with PDT. Tumor regrowth after this point resulted in an increase in dysphagia to Grade 4. The patient was retreated (Course 2) with PDT and an improvement in dysphagia to Grade 1 was achieved. The patient experienced joint pain (Grade 3) for 3 days during this course. The patient was seen 1 week after the Month-1 endoscopy, at which time dysphagia had worsened to Grade 4. However on this day, the patient experienced an event of hematemesis that resulted in death. This event was considered by the investigator as not associated with the study treatment.

Legend: CR Complete Remission D Debridement E Endoscopy L Laser Light Application LTF Lost to Follow-up NE Not Evaluable O Off Study PD Progressive Disease P PHOTOFRIN Injection PR Partial Remission SD Stable Disease X Endoscopy & Dilatation

Figure 6: Graphic Presentation of Efficacy and Safety for Patient

Age: 77
Gender: Female
Histology: Adenocarcinoma
Tumor Length: 4 cm

Tumor Location: Lower Third
Submucosal Involvement: None
Prior Therapy: No
PHOTOFRIN Formulation: Frozen



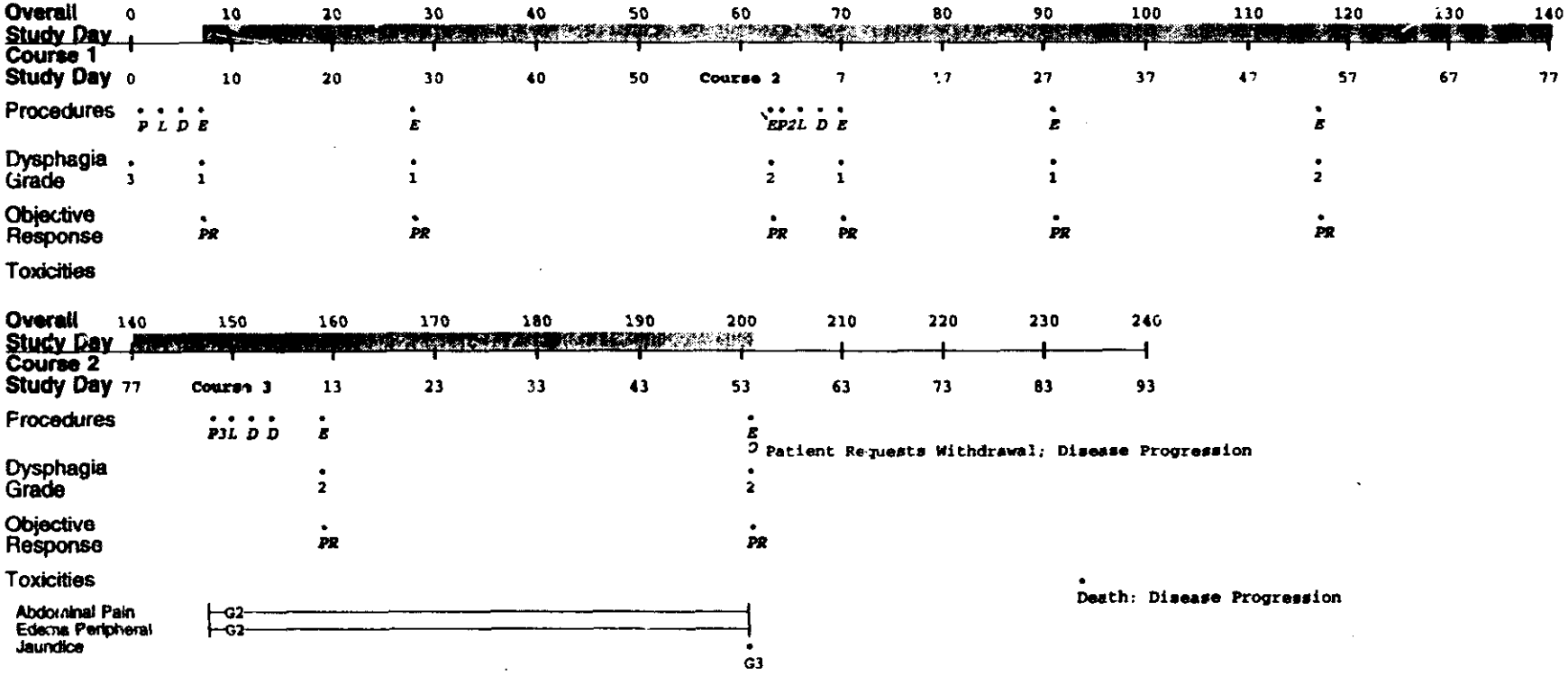
Patient had a 4-cm esophageal tumor with a baseline dysphagia of Grade 4. The patient had metastatic disease to the colon and lungs. Following PDT, the patient experienced a three-grade improvement in dysphagia to Grade 1 at Week 1. The change in esophageal luminal diameter corresponded to a partial response. This improvement in dysphagia and objective response was maintained at the Month-1 and Month-2 assessments. Three months after starting PDT, the patient experienced an event of respiratory failure (Grade 4) which resulted in death. The event was considered by the investigator to be not related to study therapy. No other adverse events of Grade 3 or greater were observed during the study.

Legend: CR Complete Remission D Debridement E Endoscopy L Laser Light Application LTF Lost to Follow-up NE Not Evaluable O Off Study PD Progressive Disease P PHOTOFRIN Injection PR Partial Remission SD Stable Disease X Endoscopy & Dilatation

Figure 11: Graphic Presentation of Efficacy and Safety for Patient

Age: 63
Gender: Male
Histology: Adenocarcinoma
Tumor Length: 10 cm

Tumor Location: Lower Third
Submucosal Involvement: None
Prior Therapy: Yes
PHOTOFRIN Formulation: Lyophilized



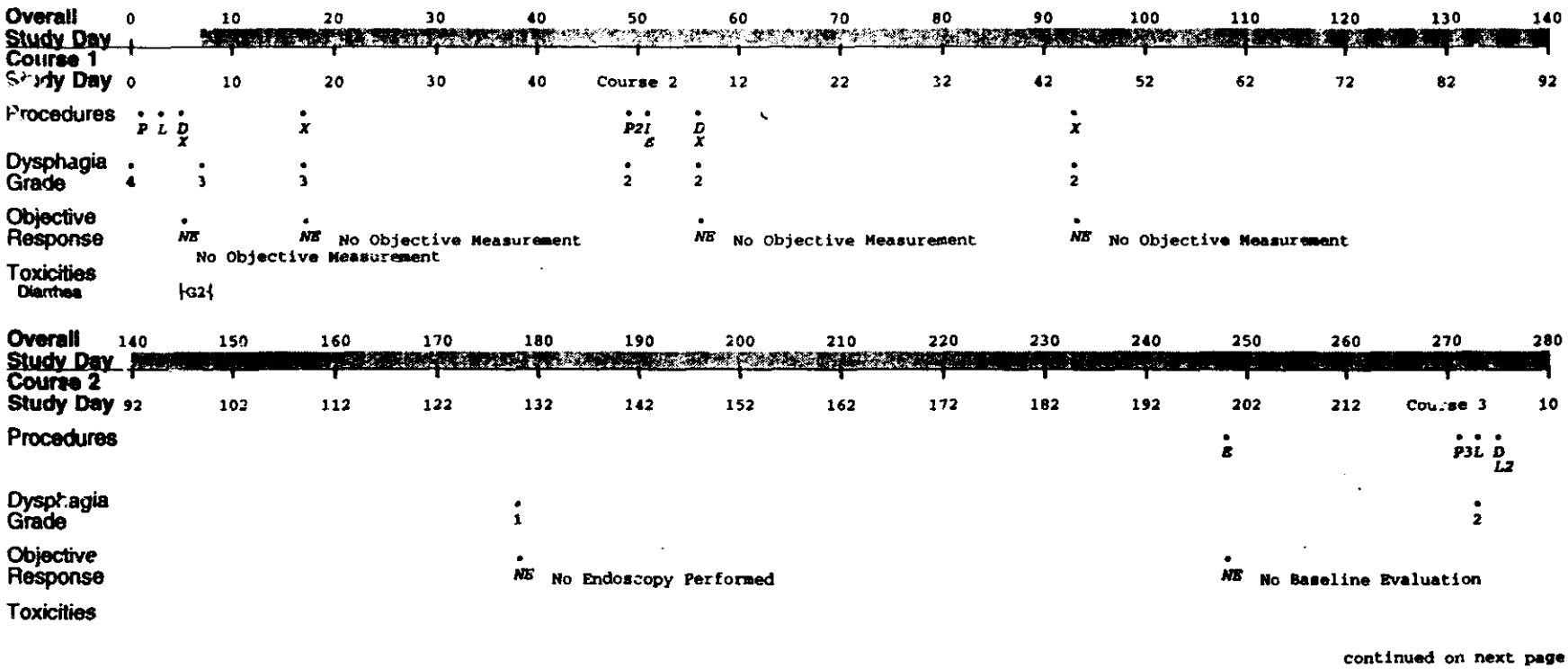
Patient presented at baseline with a 10-cm tumor and Grade 3 dysphagia. At the Week-1 assessment following PDT, the patient's dysphagia had improved to Grade 1, with a partial objective response. This response was maintained at Month 1, but dysphagia had worsened to Grade 2 by Month 2. A second course of PDT was given and dysphagia had improved to Grade 1 one week later. This response was maintained at Month 1, but again dysphagia had worsened by 1 grade at Month 2, despite a minimal change in the luminal diameter. A third course of PDT was given, but dysphagia remained unchanged. However, based on the change in esophageal lumen from baseline, the objective response throughout all three courses indicated a partial response. One month after the start of Course 3, the patient developed Grade 3 jaundice and was taken off study due to liver metastases and patient request. No other adverse events of Grade 3 or greater occurred during the 3 courses. The patient died approximately 1 month later of disease progression.

Legend: CR Complete Remission D Debridement E Endoscopy L Laser Light Application LTF Lost to Follow-up NE Not Evaluable O Off Study PD Progressive Disease P PHOTOFRIN Injection PR Partial Remission SD Stable Disease X Endoscopy & Dilatation

Figure 14: Graphic Presentation of Efficacy and Safety for Patient

Age: 79
Gender: Male
Histology: Squamous Cell Carinoma
Tumor Length: 10 cm

Tumor Location: Lower Third
Submucosal Involvement: None
Prior Therapy: No
PHOTOFRIN Formulation: Frozen



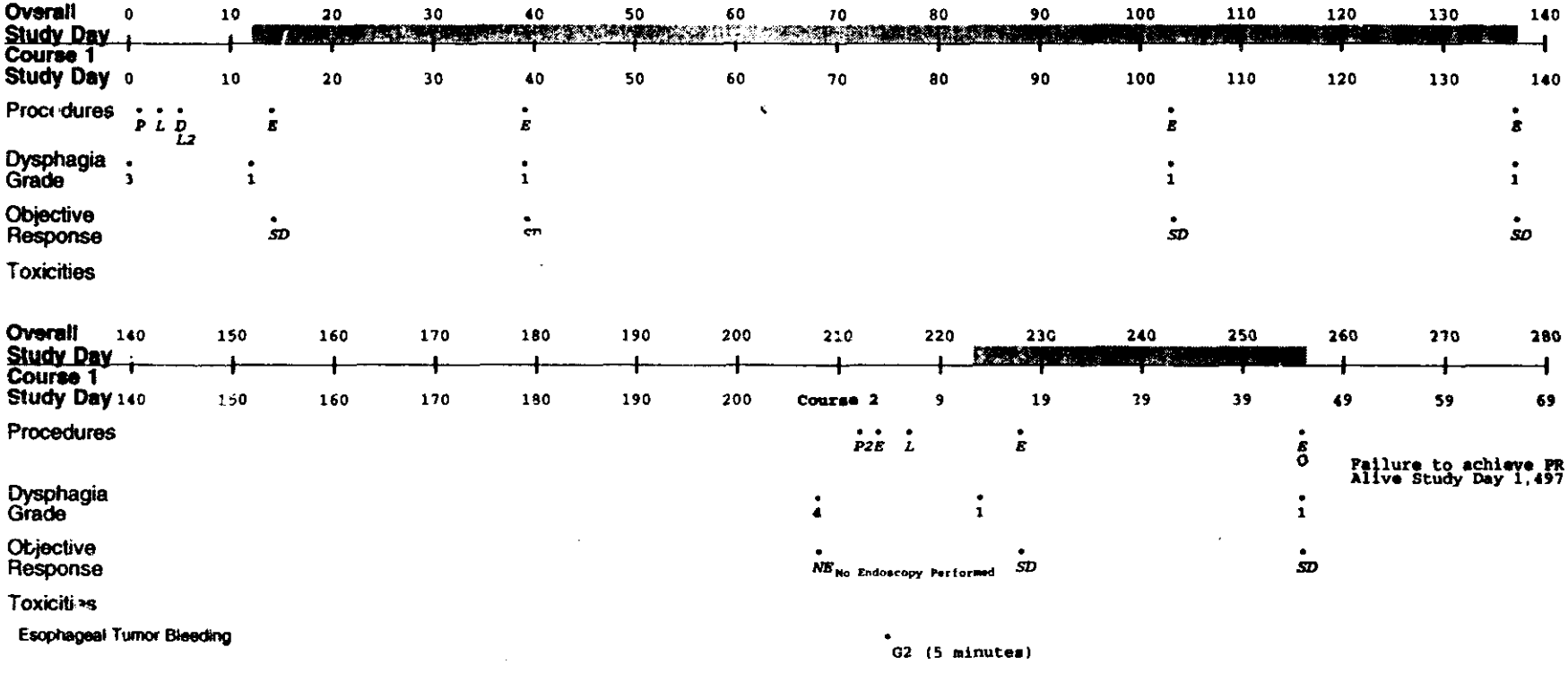
continued on next page

Legend: CR Complete Remission D Debridement E Endoscopy L Laser Light Application LTF Lost to Follow-up NE Not Evaluable O Off Study PD Progressive Disease P PHOTOFRIN Injection PR Partial Remission SD Stable Disease X Endoscopy & Dilatation

Figure 16: Graphic Presentation of Efficacy and Safety for Patient

Age: 87
Gender: Male
Histology: Adenocarcinoma
Tumor Length: 6 cm

Tumor Location: Middle Third
Submucosal Involvement: None
Prior Therapy: No
PHOTOFRIN Formulation: Frozen



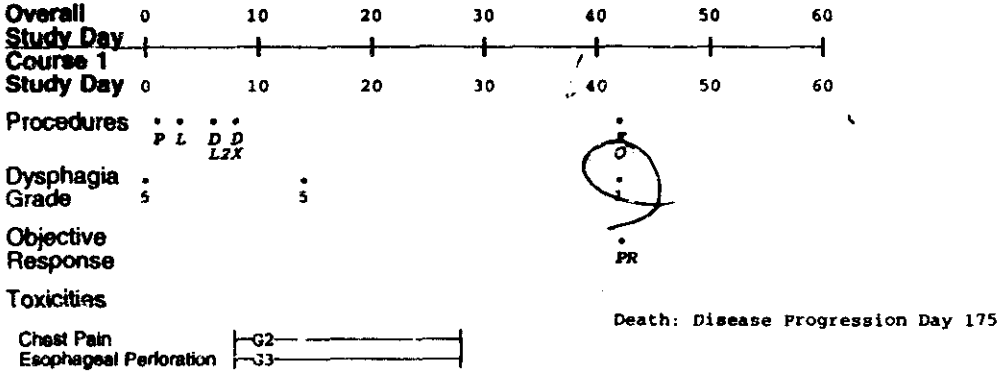
Patient presented at baseline with a 6-cm tumor and Grade 3 dysphagia. At the Week-1 post-PDT assessment, dysphagia had improved to Grade 1 but the objective response indicated stable disease. This response was maintained until the Month-6 assessment, at which time the patient was found to have Grade 4 dysphagia. A second course of PDT was given: both the Week-1 and Month-1 assessments indicated an improvement in dysphagia to Grade 1. The minimal change in esophageal luminal diameter indicated an objective response of stable disease at both visits. The patient was taken off study at the Month-1 visit of Course 2 due to failure to achieve a partial response. There were no adverse events of Grade 3 toxicity or greater, and the patient was still alive 4 years after the study start.

Legend: CR Complete Remission D Debridement E Endoscopy L Laser Light Application LTF Lost to Follow-up NE Not Evaluable O Off Study PD Progressive Disease P PHOTOFRIN Injection PR Partial Remission SD Stable Disease X Endoscopy & Dilatation

Figure 26: Graphic Presentation of Efficacy and Safety for Patient

Age: 79
Gender: Female
Histology: Squamous Cell Carcinoma
Tumor Length: 22 cm

Tumor Location: Upper Third
Submucosal Involvement: Yes
Prior Therapy: No
PHOTOFRIN Formulation: Frozen



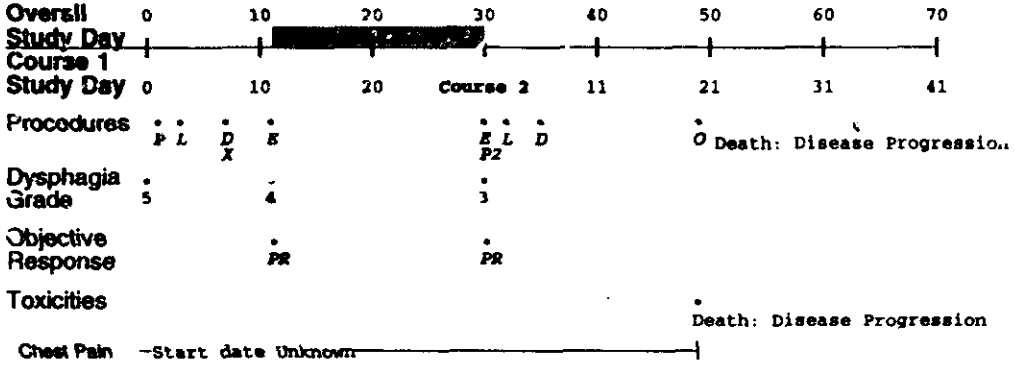
Patient presented at baseline with a 22-cm tumor and Grade 5 dysphagia. The patient was treated with PDT and received two laser light treatments. During tumor debridement 2 days after the second laser light treatment, the patient developed a Grade 3 esophageal perforation that was considered related to the study treatment. The Week-1 visit indicated no improvement in dysphagia. At the Month-1 assessment, dysphagia had improved by four grades to Grade 1, with a partial objective response. At this time, however, the investigator took the patient off study. The patient died 4 months later due to disease progression.

Legend: CR Complete Remission D Debridement E Endoscopy L Laser Light Application LTF Lost to Follow-up NE Not Evaluable O Off Study
PD Progressive Disease P PHOTOFRIN Injection PR Partial Remission SD Stable Disease X Endoscopy & Dilatation

Figure 27: Graphic Presentation of Efficacy and Safety for Patient

Age: 60
Gender: Female
Histology: Squamous Cell Carcinoma
Tumor Length: Unknown

Tumor Location: Upper Third
Submucosal Involvement: Unknown
Prior Therapy: Yes
PHOTOFRIN Formulation: Frozen



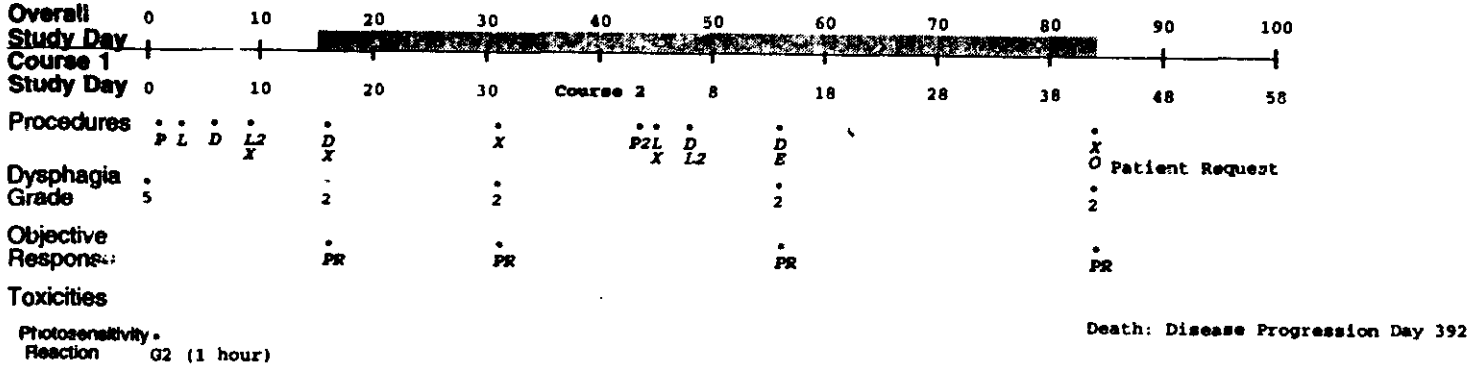
Patient was enrolled in Study P20 with Grade 5 dysphagia. She received one laser light application following PHOTOFRIN® injection, which resulted in an improvement in dysphagia at Week 1 to Grade 4 and a partial objective response. Dysphagia had further improved at Month 1 to Grade 3. At this time, the investigator decided to administer a second course of PDT. Unfortunately, the patient died 2 weeks after the last treatment endoscopy due to disease progression. This event was considered by the investigator to be unrelated to the study treatment. During both PDT courses, the patient did not experience any toxicities of Grade 3 or greater.

Legend: CR Complete Remission D Debridement E Endoscopy L Laser Light Application LTF Lost to Follow-up NE Not Evaluable O Off Study
PD Progressive Disease P PHOTOFRIN Injection PR Partial Remission SD Stable Disease X Endoscopy & Dilatation

Figure 28: Graphic Presentation of Efficacy and Safety for Patient

Age: 54
Gender: Female
Histology: Squamous Cell Carcinoma
Tumor Length: Unknown

Tumor Location: Upper Third
Submucosal Involvement: None
Prior Therapy: Yes
PHOTOFRIN Formulation: Frozen



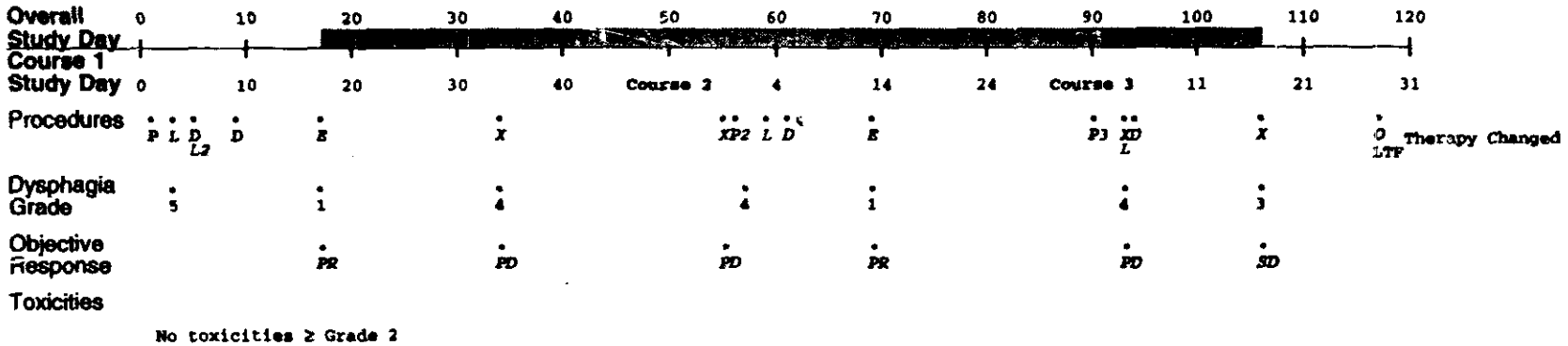
Patient was enrolled in Study P20 with Grade 5 dysphagia. One week following PDT, the patient's dysphagia had improved to Grade 2, with a partial objective response. The smallest esophageal luminal diameter had increased from 0.2 cm at baseline to 1.5 cm at this visit. This improvement in dysphagia and objective response was maintained at the Month-1 assessment, despite a narrowing of the esophageal lumen. Due to the lumen decrease, the investigator initiated a second course of PDT. The Week-1 assessment indicated that dysphagia was unchanged at Grade 2 with a partial objective response. This response was maintained at the Month-1 visit. The patient was removed from the study at this visit at the request of the patient. During both courses of PDT, the patient did not experience any toxicities of Grade 3 or greater. A survival follow-up indicated that the patient died due to disease progression 10 months after leaving the study.

Legend: CR Complete Remission D Debridement E Endoscopy L Laser Light Application LTF Lost to Follow-up NE Not Evaluable O Off Study PD Progressive Disease P PHOTOFRIN Injection PR Partial Remission SD Stable Disease X Endoscopy & Dilatation

Figure 29: Graphic Presentation of Efficacy and Safety for Patient

Age: 84
Gender: Male
Histology: Squamous Cell Carcinoma
Tumor Length: Unknown

Tumor Location: Middle Third
Submucosal Involvement: None
Prior Therapy: No
PHOTOFRIN Formulation: Lyophilized



Patient presented at baseline with Grade 5 dysphagia. One week following PDT, dysphagia had improved by four grades to Grade 1, with a partial objective response. However, by Month 1, the esophageal disease had progressed, with dysphagia worsening to Grade 4. This response was unchanged at Month 2, so the investigator administered a second course of PDT. One week following this second course, dysphagia had improved to Grade 1. Again, however, rapid tumor regrowth resulted in a worsening of dysphagia to Grade 4 at Month 1. A third course of PDT was given, but the response to treatment was minimal. Dysphagia improved to Grade 3 at Week 1, but the objective response indicated stable disease. The patient was taken off study and received alternate therapy. The patient was subsequently lost to follow-up. At no time during the three courses of PDT did the patient experience any toxicities of Grade 2 or greater.

Legend: CR Complete Remission D Debridement E Endoscopy L Laser Light Application LTF Lost to Follow-up NE Not Evaluable O Off Study
PD Progressive Disease P PHOTOFRIN Injection PR Partial Remission SD Stable Disease X Endoscopy & Dilatation

Medical Officer Review #3 (Photofrin)

1.0 General Information:

1.1 NDA# 20-451
1.1.2 Review: M.O. Review #3
1.1.3 Submission date: April 14, 1994
1.1.4 Date of Review December 20, 1994

1.2 Drug Name
1.2.1 Generic name: Sterile porfimer sodium
1.2.2 Trade name: Photofrin

1.3 Applicant: Quadralogic Technologies Inc.

1.4 Pharmacologic Category: Photosensitizer, antineoplastic agent

1.5 Proposed indication: Complete or partially obstructing esophageal cancer.

In the appendix of this review is a Memorandum and draft review of the Chemistry Scheme issue. This document was sent to the Applicant on September 7, 1994. Subsequently there has been an advisory committee meeting at which time limited approval was recommended. The Sponsor responded to the issues in a October 21 submission. The topics in this review will be:

- Review of 9/6/94 reviewer memo/draft review of reviewer analyses sent to the applicant regarding Scheme
- Review of applicant's response.
- Review of ODAC recommendations.
- Review of major labeling deficiencies.
- Recommendations.

1. **Reviewer Analyses:**

The most relevant comparison is to compare patients who received the lyophilized formulation, and either scheme or scheme The following are extracted from page 4 of the appendix:

	Lyophil.,Scheme	Lyophil., Scheme
1-month Dysphagia response(# and %)	14/31 (45%)	6/27 (22%)
Grade 3 or 4 toxicity (# and %)	17/31 (55%)	15/27 (56%)

In the study of completely obstructed esophageal cancer, of those with data on formulation, response was seen in 3/7 patients with scheme and 3/5 with scheme

Page 7 of the appendix lists adverse events of patients receiving lyophilized formulation by manufacturing scheme. In 31 patients receiving scheme there were 214 events for an average of 6.9 events per patient. In the 27 patients receiving scheme there were 217 events for an average of 8.0 events per patient. Most of the excess events in the scheme group are grade I and grade II.:

Normalized:(#AEs) / (#Pts with Process)

	Grade I	Grade II	Grade III	Grade IV	Any Grades
Scheme (31 pts)	3.23	2.19	0.9	0.32	6.9
Scheme (27 pts)	3.74	2.81	1.11	0.33	8.04

Examination of the tables in pp 8-10 of the appendix show that much of the excess in adverse events in the scheme group in the can be accounted for by the excess in Gastrointestinal events:

	Number of GI events	Number of Patients	Events/Patient
Scheme	38	31	1.23
Scheme	69	27	2.56

Reviewer comments

The above analysis was retrospective, historical, and unplanned. Findings could be attributed to one of several factors beside the change in manufacturing scheme: multiple exploratory analyses may yield positive results simply because of the multiplicity of analyses; statistically significant differences could be due to changes in patient characteristics with time or due to changes in investigator practices with time.

On the other hand, the data cannot be considered supportive that the clinical results with scheme are similar to that with scheme If such assurance was required, it would have to come from some other source such as a concurrent comparative trial in animals or in man.

2. QLT 10/21/94 response:

a. Chemical batch analyses and theoretical considerations

In an early step in photofrin synthesis, hematoporphyrin diacetate is treated with N NaOH. In Scheme , this treatment with base lasted In scheme the treatment with base was extended to to favor the formation of over linkages.

Examination of table 1 of the submission shows that scheme batches contained from % of whereas scheme batches contained from % The calculated amounts of per vial was similar mg/vial on scheme and on scheme . All batches produced similar activity in bioassay: % tumor cure with scheme versus % tumor cure with scheme .

The applicant discusses the potential clinical significance of a difference in fraction of bonds. One possibility is that the bonds would be hydrolyzed in the body, leaving less active photofrin for activation at the time of light application. Since the batches administered in the study had similar amounts of calculated linked porphyrins mg/vial), this is not likely to explain any differences seen in the trial.

The sponsor also shows that oligomer distribution (dimer, trimer, etc.) was similar in batches from of the two schemes (see attached graph).

The sponsor summarizes that the changes in manufacturing should not have been clinically significant: the change in content were minor and oligomer distribution were similar.

b. Clinical Data

i. Efficacy

The applicant examined the data according to scheme PDT received. Of the patients receiving lyophilized product, 20 received scheme and 26 scheme A concurrent control population on the YAG arm was identified at each site. Table 5 shows the change from baseline in course 1. These were similar at week 1 and at month one. Response assessment based on dysphagia grade are shown in the applicant's table 6. Whereas response was similar at one week (42% vs 45%), response was higher in the scheme group at 1 month (45% vs 19%).

Dysphagia response, Week 1

	Scheme	Scheme
PDT	9 (45%)	11 (42%)
YAG	12 (57%)	8 (36%)

Dysphagia response, Month 1

	Scheme	Scheme
PDT	9 (45%)	5 (19%)
YAG	5 (24%)	6 (27%)

Objective response rates as noted by the sponsor are summarized in the following table

Objective response, Week 1

	Scheme	Scheme
PDT	12 (60%)	7 (27%)
YAG	10 (48%)	7 (32%)

Objective response, Month 1

	Scheme	Scheme
PDT	7 (35%)	8 (31%)
YAG	4 (19%)	2 (9%)

In an effort to explain the lower response rate when scheme was used, the sponsor examined the distribution of centers entering patients at times when the different schemes were administered. It was noted that several centers with higher response rates enrolled fewer patients during the later time when scheme was used; most notably center 8 which enrolled 1/5 of the study patients overall only enrolled 2 patients during the time when scheme photofrin was used. This center had a very high one-month objective response rate of 74% (17/23) on the PDT arm. The applicant attributes the higher response rate at this center to a combination of investigator experience and favorable baseline prognostic factors.

ii. Safety

The applicant's summary of adverse events classified by photofrin formulation received is presented in table 10 (attached). The only events noticeably more common in the Scheme group are constipation (38% vs 11%) and abdominal pain (35% vs 11%). These events occurred together in 7 patients. Although anemia and pleural effusion were more common with the later lyophilized formulation, no difference was apparent between the scheme and scheme manufacturing scheme.

The applicant's attached table 11 examines the severity of adverse event by manufacturing scheme; it demonstrates that the difference in event frequency between scheme and scheme was primarily due to a difference in Grade 2 reactions (45% vs 26%) rather than Grade 3 (31% vs 30%) or Grade 4 (29% vs 22%).

The applicant concludes that the safety profiles are similar for Scheme and Scheme

The applicant then addresses the question of whether the changes in side-effects seen with the switch to the lyophilized formulation were actually due to a difference in manufacturing scheme. Adverse events more common with the lyophilized formulation are listed in the applicant's table 12 (attached). Of the 9 events, 6 appeared similar in the schemes and 3 appeared more frequent in scheme The 3 more common with scheme were abdominal pain and constipation as mentioned above, and Esophageal tumor bleeding (17% vs 0%; 5 events versus no events). However, one notes that there was also a higher rate of esophageal tumor bleeding on the laser control arm during the time of Scheme than during the time of Scheme (13% vs 0%; 3 events versus none).

iii Information from investigators

The applicant solicited information from preclinical investigators on whether they noted a change in photofrin performance at the time when Scheme was introduced.

2 of the investigators had suitable comparative evidence, and many others had a more subjective opinion.

On p 0116 of the submission, data from Dr. Oriold Dereski at Henry Ford Hospital is presented. Dr. Dereski was studying depth of PDT induced brain necrosis on normal rat brain:

Time period (scheme)	Depth of Necrosis
March to June 1991 (Scheme	2.97 +/- 0.48
March to April 1993 (Scheme	3.02 +/- 0.67

On p 117 data is presented from Dr. Tom Dougherty at Roswell Park on his standard antitumor bioassay:

Time period (scheme)	% tumor response at 7 days
July to October, 1991	84 +/- 23
March to June, 1993	91.5 +/- 12

There are several other verbal testimonials from investigators studying pdt use in various animal models that they have seen no difference over the time spanning the change from scheme to scheme

Reviewer Conclusion on Clinical Data analyzed by Manufacturing Scheme.

A retrospective historical comparison of results was performed in 2 groups of patients, each of whom had received the lyophilized formulation but who had received photofrin manufactured by scheme versus photofrin manufactured by scheme There were about 30 such patients in each group. There was a trend toward a lower response rate and a trend toward greater incidence of adverse reactions in the more recently treated patients, the group receiving PDT produced with Manufacturing scheme The most significant difference in adverse reactions was noted in the gastrointestinal category (constipation and abdominal pain). Excess reactions were primarily grade II.

In my opinion these uncontrolled data do not represent strong evidence, either positive or negative, of whether Scheme and Scheme would produce similar or different clinical outcomes. Certainly responses were seen in both groups and no new toxicities were noted.

3. Findings of the 9-12-94 Oncologic Drugs Advisory Committee

The committee voted 12 to 0 that the results demonstrate that PDT with photofrin can increase the luminal diameter in patients with partially obstructing esophageal cancer. The committee voted 11 to 1 that photofrin was approvable for patients who, in the opinion of their physician, cannot be satisfactorily treated with YAG because of, for example, obstructing lesions or proximal, flat or angulated tumors. The committee voted 7 to 5 against general approval for partially obstructing esophageal cancer.

4. Review of Draft Labeling

The following comments refer by number to areas which are highlighted in the draft labelling in the appendix of this review.

1. The asterisk for statistical significance should be removed. The column with Time to palliation failure should be removed. Either text or table should mention that the amount of missing data prohibited a statistical comparison of efficacy on the 2 arms.

   Data on one-month dysphagia grade changes should be included as part of the efficacy presentation.

2. This should be replace by "palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the

opinion of their physician, should not be treated with ND-YAG laser therapy."

3. This statement is too dogmatic, we don't have sufficient data to say safety and efficacy is equivalent in the young and the old.

4. I would remove this section on endobronchial carcinoma.

5. 4-month Safety Update (Document data 8-12-94)

The 4-month safety update includes data from a few more patients than presented in the NDA, in studies of various indications. No new safety findings of significance are noted.

Reviewer Recommendations:

The Applicant will be meeting with the Agency in January.

At the Agency pre-meeting, I suggest that we answer the following inter-disciplinary questions. The questions pre-suppose that the clinical data on safety and efficacy of scheme are not definitive in either a positive or negative sense.

- Are the differences in Scheme and Scheme of such significance that bridging studies are necessary?
- If so, what sort of studies would suffice?
- If bridging studies are needed could the Scheme I product be approved in the interim?

  -Could the company make the scheme product?

  -Would it be approvable from a chemistry perspective?

Grant A. Williams, M.D.

cc: HFD 150 GWilliams, CSO
Application: NDA 20-451

TABLE 1. Batch Analyses for Clinical Batches Used in Study P19

MRD Batch Number	Clinical Supplies Batch Ref. No.	Date of Manufacture	Formulation	Synthetic Scheme	Porfimer Sodium Content (mg/vial)	% Ester (HPLC)	Calculated "Porfimer Ethers"[a] (mg/vial)	Bioassay % Tumor Cure	Number of Patients in Study P19
PC 253C		1/21/88	Frozen		79.3	NA	-	80%	2
PC 256C		3/3/88	Frozen		76.3	NA	-	80%	8
PC 258C		4/1/88	Frozen		72.5	NA	-	90%	1
PC 260C		4/21/88	Frozen		79.8	NA	-	80%	10
PC 264C		6/29/88	Frozen		75.3	NA	-	80%	2
PC 265C		7/7/88	Frozen		75.0	NA	-	100%	2
PC 266C		7/17/88	Frozen		72.2	NA	-	pass[c]	5
PC 267C		8/4/88	Frozen		70.8	NA	-	80%	2
PC 271C		10/88	Frozen		NA	NA	-	NA	4
PC 272C		10/13/88	Frozen		76.3	NA	-	pass[c]	3
PC 273J		3/15/89	Frozen		80.9	11.4[b]	71.7	70%	0
PC 274J		4/12/89	Frozen		79.8	9.6[b]	72.1	80%	5
PC 275J		7/13/89	Frozen		81.7	NA	-	100%	2
6894B15A		3/31/89	Lyophilized		85.8	13.4	70.0	80%	28
B90-120-0043		3/22/90	Lyophilized		76.3	8.6	69.7	100%	18
K90-120-0186		11/7/90	Lyophilized		78.2	6.6	73.0	80%	22
I91-111-010		9/30/91	Lyophilized		77.5	3.1	75.1	97%	5

[a] "Porfimer ethers" refers to the amount of porfimer sodium not susceptible to hydrolysis.
[b] Mean values from stability program, stored at -20°C (individual data in Appendix 1)
[c] "pass" means tumor cure in at least 5 of 10 mice
NA = not available

? % Ethers

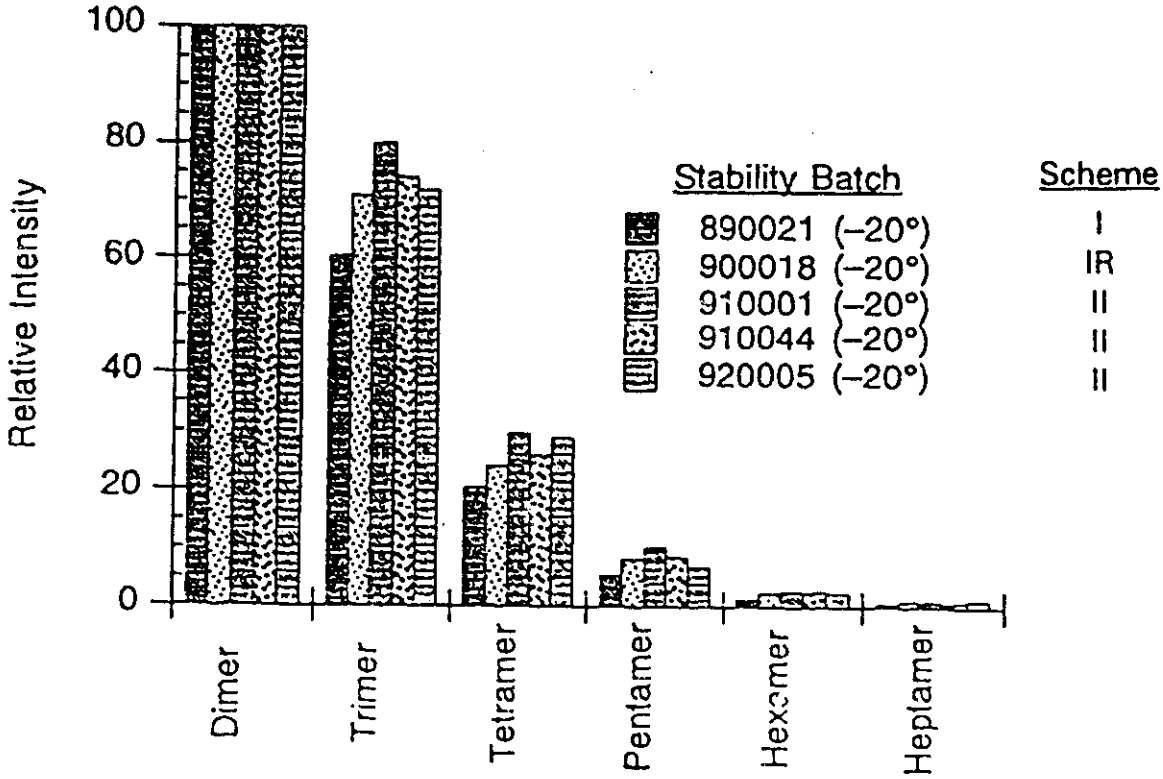


FIGURE 1. Relative Peak Intensities for Oligomers (normalized to dimer intensity) in Five Batches of PHOTOFRIN Sterile Porfimer Sodium as determined by FAB Mass Spectrometry

TABLE 5. Course 1 Mean Changes in Dysphagia Grade from Baseline by PHOTOFRIN® Manufacturing Scheme

Number (%) of Patients

	Frozen	Lyophilized		
Scheme	I	I	IR	II
	n=42	n=21	n=17	n=22
WEEK 1				
Number of Patients				
PDT	33	19	16	22
Nd:YAG[a]	38	20	15	15
Mean Change from Baseline				
PDT	-1.15 *	-0.53	-0.44	-0.41
Nd:YAG	-1.13 *	-0.80 *	-0.47	-0.87 *
MONTH 1				
Number of Patients				
PDT	29	15	12	14
Nd:YAG	26	13	12	14
Mean Change from Baseline				
PDT	-0.93 *	-0.67 *	-0.58 *	-0.57 *
Nd:YAG	-0.69 *	-0.46	-0.75 *	-0.5

[a] concurrent Nd:YAG-treated patients
* significant improvement from baseline

TABLE 6. Course 1 Response Assessments Based on Improvements in Dysphagia Grades by PHOTOFRIN® Manufacturing Scheme

All Treated Patients

Number (%) of Patients

	Frozen	Lyophilized		
Scheme	I	I	IR	II
Number of Patients				
PDT	43	20	16	26
Nd:YAG*	42	21	17	22
Responders				
Any Assessment				
PDT	27 (63)	12 (60)	9 (56)	13 (50)
Nd:YAG	27 (64)	12 (57)	10 (59)	10 (45)
Week 1				
PDT	22 (51)	9 (45)	7 (44)	11 (42)
Nd:YAG	27 (64)	12 (57)	7 (41)	8 (36)
Month 1				
PDT	18 (42)	9 (45)	6 (38)	5 (19)
Nd:YAG	14 (33)	5 (24)	6 (35)	6 (27)
Nonresponders				
PDT	10 (23)	8 (40)	7 (44)	12 (46)
Nd:YAG	12 (29)	8 (38)	6 (35)	8 (36)
Missing				
PDT	6 (14)	0 (0)	0 (0)	1 (4)
Nd:YAG	3 (7)	1 (5)	1 (6)	4 (18)

* concurrent Nd:YAG-treated patients

TABLE 8. Course 1 Month 1 Objective Tumor Response by PHOTOFRIN® Manufacturing Scheme

All Treated Patients

Number (%) of Patients

	Frozen	Lyophilized		
Scheme	I	I	IR	II
Number of Patients				
PDT	43	20	16	26
Nd:YAG*	42	21	17	22
CR + PR				
PDT	15 (35)	7 (35)	7 (44)	8 (31)
Nd:YAG	12 (29)	4 (19)	6 (35)	2 (9)
SD + PD				
PDT	13 (30)	5 (25)	5 (31)	5 (19)
Nd:YAG	7 (17)	8 (38)	5 (29)	12 (55)
Missing				
PDT	15 (35)	8 (40)	4 (25)	13 (50)
Nd:YAG	23 (55)	9 (43)	6 (36)	8 (36)

* concurrent Nd:YAG-treated patients

TABLE 10. Adverse Events by PHOTOFRIN® Manufacturing Scheme

Number (%) of Patients

	Frozen	Lyophilized		
Scheme	I	I	IR	II
Number of Patients				
PDT	43	27	18	29
Nd:YAG[a]	42	24	17	24
Photosensitivity				
PDT	7 (16)	6 (22)	4 (22)	4 (14)
Constipation				
PDT	7 (16)	3 (11)	4 (22)	11 (38)
Nd:YAG	3 (7)	3 (13)	1 (6)	3 (13)
Abdominal Pain				
PDT	5 (12)	3 (11)	3 (17)	10 (35)
Nd:YAG	7 (17)	1 (4)	0 (0)	3 (13)
Fever				
PDT	13 (30)	11 (41)	6 (33)	6 (21)
Nd:YAG	7 (17)	1 (4)	2 (12)	1 (4)
Pleural Effusion				
PDT	7 (16)	9 (33)	4 (22)	10 (35)
Nd:YAG	3 (7)	0 (0)	0 (0)	2 (8)
Anemia				
PDT	4 (9)	9 (33)	7 (39)	10 (34)
Nd:YAG	3 (7)	4 (17)	2 (12)	4 (17)
Atrial Fibrillation				
PDT	1 (2)	5 (19)	3 (17)	1 (3)
Nd:YAG	3 (7)	2 (8)	0 (0)	0 (0)
Inflammatory Reaction				
PDT	21 (49)	16 (59)	10 (56)	19 (66)
Nd:YAG	16 (38)	7 (29)	3 (18)	9 (38)
Respiratory Insufficiency				
PDT	5 (12)	1 (4)	2 (11)	3 (10)
Nd:YAG	0 (0)	0 (0)	1 (6)	0 (0)

[a] concurrent Nd:YAG-treated patients

TABLE 11. Severity of Adverse Events by PHOTOFRIN® Manufacturing Scheme
Number (%) of Patients

	Frozen	Lyophilized		
Scheme	I	I	IR	II
Number of Patients				
PDT	43	27	18	29
Nd:YAG*	42	24	17	24
Mild				
PDT	4 (9)	3 (11)	2 (11)	0 (0)
Nd:YAG	3 (7)	4 (17)	2 (12)	4 (17)
Moderate				
PDT	11 (26)	7 (26)	5 (28)	13 (45)
Nd:YAG	13 (31)	2 (8)	4 (24)	7 (29)
Severe				
PDT	4 (9)	8 (30)	3 (17)	9 (31)
Nd:YAG	12 (29)	7 (29)	2 (12)	9 (38)
Very Severe				
PDT	13 (30)	6 (22)	6 (33)	7 (29)
Nd:YAG	7 (17)	4 (17)	4 (24)	1 (4)

* concurrent Nd:YAG-treated patients

The incidence of very severe events was comparable across all four PDT groups. The combined incidence of severe and very severe events was also the same regardless of manufacturing scheme.

Therefore, based on the above evaluations, the safety profile appears to be the same for Scheme I, Scheme IR, and Scheme II PHOTOFRIN.

The third question raised in MOR#3 was whether the differences noted between the toxicity profile of the frozen and lyophilized products were really due to the change in manufacturing scheme. Table 12 lists the adverse events that occurred at higher frequencies with the lyophilized formulation (all schemes combined). The incidence

0021

is presented for each individual scheme and the incidence in the concurrent Nd:YAG-treated patients is also displayed.

TABLE 12. Adverse Events Occurring More Frequently with the Lyophilized Formulation

(Page 1 of 2)

Number (%) of Patients

Scheme	Frozen	Lyophilized			Lyophilized
	I	I	IR	II	All combined
Number of Patients					
PDT	43	27	18	29	74
Nd:YAG*	42	24	17	24	65
Anorexia					
PDT	0 (0)	1 (4)	1 (6)	3 (10)	5 (7)
Nd:YAG	2 (5)	0 (0)	2 (12)	2 (8)	4 (6)
Nausea					
PDT	6 (14)	6 (22)	4 (22)	6 (21)	16 (22)
Nd:YAG	9 (21)	3 (13)	2 (12)	3 (13)	8 (12)
Abdominal Pain					
PDT	5 (12)	3 (11)	3 (17)	10 (34)	16 (22)
Nd:YAG	7 (17)	1 (4)	0 (0)	3 (13)	4 (6)
Esophageal Edema					
PDT	0 (0)	1 (4)	2 (11)	4 (14)	7 (9)
Nd:YAG	1 (2)	1 (4)	0 (0)	0 (0)	1 (2)
Constipation					
PDT	7 (16)	3 (11)	4 (22)	11 (38)	18 (24)
Nd:YAG	3 (7)	3 (13)	1 (6)	3 (13)	7 (11)
Esophageal Tumor Bleeding					
PDT	1 (2)	0 (0)	1 (6)	5 (17)	6 (8)
Nd:YAG*	2 (5)	0 (0)	0 (0)	3 (13)	3 (5)

* concurrent Nd:YAG-treated patients

TABLE 12. Adverse Events Occurring More Frequently with the Lyophilized Formulation

(Page 2 of 2)

Number (%) of Patients

	Frozen	Lyophilized			Lyophilized
Scheme	I	I	IR	II	All combined
Atrial Fibrillation					
PDT	1 (2)	5 (19)	3 (17)	1 (3)	9 (12)
Nd:YAG	3 (7)	2 (8)	0 (0)	0 (0)	2 (3)
Dyspnea					
PDT	4 (9)	6 (22)	3 (17)	6 (21)	15 (20)
Nd:YAG	6 (14)	6 (25)	2 (12)	3 (13)	11 (17)
Pleural Effusion					
PDT	7 (16)	9 (33)	4 (22)	10 (34)	23 (31)
Nd:YAG	3 (7)	0 (0)	0 (0)	2 (8)	2 (3)
Anemia					
PDT	4 (9)	9 (33)	7 (39)	10 (34)	26 (35)
Nd:YAG	3 (7)	4 (17)	2 (12)	4 (17)	10 (15)
Weight Decrease					
PDT	0 (0)	6 (22)	2 (11)	0 (0)	8 (11)
Nd:YAG	0 (0)	0 (0)	1 (6)	1 (4)	2 (3)
Confusion					
PDT	0 (0)	2 (7)	2 (11)	2 (7)	6 (8)
Nd:YAG	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)
Back Pain					
PDT	0 (0)	3 (11)	2 (11)	2 (7)	7 (9)
Nd:YAG	1 (2)	0 (0)	1 (6)	1 (4)	2 (3)

[a] concurrent Nd:YAG-treated patients

(See forwarded 9/7/94)

MEMORANDUM

TO: Paul Zimmerman, CSO

From: Grant Williams, MD

Re: NDA 20-451, Clinical significance of Manufacturing change, Scheme _

Please send by FAX transmission this memo and the attached draft of text and tables which I am working on for Medical Officer Review #3.

The main topic of this review will be the clinical significance of the changes made in the manufacturing schema of the drug product. Patients from the pivotal NDA studies were treated with drug from several different schema The scheme for the drug for which marketting approval is sought is scheme

I started analyzing this problem using the list of patient numbers which were faxed to us recently in conjuction with the electronic data which I already had. Some of my preliminary analyses are attached. There was not time to finish this before the Advisory Committee date; and I would like to see how the Applicant proposes to analyze this question. Similar analyses were presented in their analysis of the formulation (frozen vs lyophilized) issue.

The Applicant should officially be requested to address questions contained in the following excerpt from my MOR#2:

"Manufacturing issue:

An important issue which is still under review is the issue of a manufacturing change that occurred toward the end of the P19 study. This is a completely different issue from the formulation (frozen vs lyophilized) issue discussed in MOR #1 and MOR #2. The manufacturing issue will be discussed in depth in a later medical officer review after the Applicant has performed its own analyses. It will not be discussed in depth with the advisory committee at this time. Introductory comments on this topic from MOR#3 follow:

> "In addition to the change in formulation over the life of the P19 study, there were changes in manufacturing process. The 3 processes are labeled The drug substance for this NDA uses process The biggest change in process occurred with the change to This change led to a larger proportion of as opposed to in the drug substance. See Chemistry Review for details on these changes. Only 27 patients in the P19 study received drug prepared by scheme

The following will be important questions for the sponsor to consider regarding the manufacturing change:

- Given the chemical changes in drug product, how clinically significant might we expect the changes to be?
- What evidence do we have that efficacy and safety are not significantly different after the manufacturing change?
- Is the difference in toxicity profile noted concurrent with change to lyophilized formulation actually due to the concurrent manufacturing change to scheme

I do not expect to deal with this with the advisory committee, and a presentation on this issue in addition to the other complex issues involved with this NDA might unnecessarily 'cloud the water.'

4.0 Manufacturing Schema vs Data in Study P19 and P20

In addition in the change in formulation over the life of the P19 study, there has been a change in manufacturing process. The 3 processes are labeled . The drug substance for this NDA uses process The biggest change in process occurred with the change to This change led to a larger proportion of as opposed to in the drug substance. See Chemistry Review for details on these changes. Only 27 patients in the P19 study received drug prepared by scheme

P19 STUDY:

Method for analysis of data on chemical method, formulation, response, and toxicity:

Data on **formulation** was taken from SAS table VIII_C under field labeled 'drug'.

- 8 Patients with formulation not in data base (table VIIIC) were not included.
- PDT patients listed as ' 0' only in data base were listed as 'frozen' formulation.
- PDT patients listed at any time as '2' were listed as 'lyophilized' formulation.

Data on **manufacturing scheme** was taken from 6-6-94 submission.

- Patients listed as receiving Scheme at any time were listed as
- PDT patients listed as Scheme only were listed as
- Other PDT patients were listed as Scheme

Responses were counted according to dysphagia grades recorded at 'Baseline' and' month001' as analyzed in Medical Officer Review #1.

Toxicity data was take from SAS table AELIST. Patients with any Grade 3 or 4 reaction at any time were listed as YES.

A table was prepared with the information on these 4 categories for a total of 110 patients who had received PDT. The following analyses were prepared from this table:

Response and Toxicity versus Formulation and Scheme

FORMULATION	CHEM PROCESS	# Patients	# Responders	(%)	# Pts Gr 3 or 4	(%)
Lyophilized			6	38	8	50
Lyophilized			6	22	15	56
Lyophilized			14	45	17	55
Frozen			14	39	17	47

FORMULATION	# Patients	#Responders	(%)	# Pts Gr 3 or 4	(%)
Frozen		14	39	17	47
Lyophilized		26	35	40	54

CHEM PROCESS	# Patients	# Responders	(%)	# Pts Gr 3 or 4	(%)
		6	38	8	50
		6	22	15	56
		28	42	34	51
		34	41	42	51

The only comparisons of significance are those for response for Chemprocess II (22%) versus Chem process I (42%), p=0.05 or Chem process II (22%) versus all other PDT patients (Chem process I plus IR) (41%), p=0.05 by Chi square.

Further Toxicity Evaluation of P19 by Number of Adverse Events:

In MOR#1 there was much discussion about an increased rate of adverse events in the patients who received the lyophilized formulation. There are many factors that could explain this: change over time in population, investigators, techniques, or concommitant change in drug product with change in manufacturing scheme . The following analasis looks only at patients who received the lyophilized solution as identified in the data base ('2' in table VIII_C). Total number of adverse reactions are analyzed is are (number of reactions)/(total number of patients) which I have termed 'normalized.' Certainly these are not independent events for statistical analysis since some events are reported more than once in the same patient.
The following table presents adverse events by Severity Grade recorded. 31 patients received scheme I accounting for 214 adverse reactions. 27 patients received scheme accounting for 217 reactions. Normalized, these are 6.9 per patient versus 8.0 per patient.

FORMULATION	CountOfAE	CountOf PT	Normalised (events/pt)
Frozen	195	29	6.72
Lyophilized	531	69	7.7

Adverse Events by Manufacturing Process and by Grade in Patients Receiving Lyophilized Formulation of Photofrin:

# OF AEs								
	CHEM PROCESS	GRADE:	<=	Grade 1	Grade 2	Grade 3	Grade 4	Total
	(31 pts)		8	100	68	28	10	214
	(27 pts)		1	101	76	30	9	217
	(16 pts)			36	48	13	10	107
	Total							538
Normalized:(#AEs) / (#Pts with Process)								
	(31 pts)		0.26	3.23	2.19	0.9	0.32	6.9
	(27 pts)		0.04	3.74	2.81	1.11	0.35	8.04
	(16 pts)		0	2.25	3	0.81	0.63	6.69

#AEs by Scheme			
Scheme:			
APPLICATION SITE		1	
AUTONOMIC NERVOUS SYSTEM	5	2	5
BODY AS A WHOLE	48	38	20
CARDIOVASCULAR	2	2	
CENTRAL NERVOUS SYSTEM	5	5	3
GASTROINTESTINAL	38	69	32
HEARING & VESTIBULAR	2		
HEART RATE/RHYTHM	9	4	6
LIVER AND BILIARY	2	3	
METABOLIC & NUTRITIONAL	14	4	3
MUSCULO-SKELETAL	1	3	
MYO-,ENDO-,PERICARDIAL & VALVE	3	2	
PSYCHIATRIC	13	12	6
RED BLOOD CELL	10	12	5
RESISTANCE MECHANISM	7	5	2
RESPIRATORY	37	33	19
SKIN AND APPENDAGES	11	15	5
URINARY	4	7	2
VASCULAR (EXTRACARDIAC)		2	2
VISION	4	1	1

#AEs Normalized to Patient by Scheme			
Category of AE			
APPLICATION SITE		0.04	
AUTONOMIC NERVOUS SYSTEM	0.16	0.07	0.31
BODY AS A WHOLE	1.55	1.41	1.25
CARDIOVASCULAR	0.06	0.07	
CENTRAL NERVOUS SYSTEM	0.16	0.19	0.19
GASTROINTESTINAL	1.23	2.56	2.00
HEARING & VESTIBULAR	0.06		
HEART RATE/RHYTHM	0.29	0.15	0.38
LIVER AND BILIARY	0.06	0.11	
METABOLIC & NUTRITIONAL	0.45	0.15	0.19
MUSCULO-SKELETAL	0.03	0.11	
MYO-,ENDO-,PERICARDIAL & VALVE	0.10	0.07	
PSYCHIATRIC	0.42	0.44	0.38
RED BLOOD CELL	0.32	0.44	0.31
RESISTANCE MECHANISM	0.23	0.19	0.13
RESPIRATORY	1.19	1.22	1.13
SKIN AND APPENDAGES	0.35	0.56	0.31
URINARY	0.13	0.26	0.13
VASCULAR (EXTRACARDIAC)		0.07	0.13
VISION	0.13	0.04	0.06

CHEM PROCESS	CAT	AeCount	#PtsInProcess	NormalizedAeCount
	AUTONOMIC NERVOUS SYSTEM	5	31	0.16
	BODY AS A WHOLE	48	31	1.55
	CARDIOVASCULAR	2	31	0.06
	CENTRAL NERVOUS SYSTEM	5	31	0.16
	GASTROINTESTINAL	38	31	1.23
	HEARING & VESTIBULAR	2	31	0.06
	HEART RATE/RHYTHM	9	31	0.29
	LIVER AND BILIARY	2	31	0.06
	METABOLIC & NUTRITIONAL	14	31	0.45
	MUSCULO-SKELETAL	1	31	0.03
	MYO-,ENDO-,PERICARDIAL & VALVE	3	31	0.10
	PSYCHIATRIC	13	31	0.42
	RED BLOOD CELL	10	31	0.32
	RESISTANCE MECHANISM	7	31	0.23
	RESPIRATORY	37	31	1.19
	SKIN AND APPENDAGES	11	31	0.35
	URINARY	4	31	0.13
	VISION	4	31	0.13
	APPLICATION SITE	1	27	0.04
	AUTONOMIC NERVOUS SYSTEM	2	27	0.07
	BODY AS A WHOLE	38	27	1.41
	CARDIOVASCULAR	2	27	0.07
	CENTRAL NERVOUS SYSTEM	5	27	0.19
	GASTROINTESTINAL	69	27	2.56
	HEART RATE/RHYTHM	4	27	0.15
	LIVER AND BILIARY	3	27	0.11
	METABOLIC & NUTRITIONAL	4	27	0.15
	MUSCULO-SKELETAL	3	27	0.11
	MYO-,ENDO-,PERICARDIAL & VALVE	2	27	0.07
	PSYCHIATRIC	12	27	0.44
	RED BLOOD CELL	12	27	0.44
	RESISTANCE MECHANISM	5	27	0.19
	RESPIRATORY	33	27	1.22
	SKIN AND APPENDAGES	15	27	0.56
	URINARY	7	27	0.26
	VASCULAR (EXTRACARDIAC)	2	27	0.07
	VISION	1	27	0.04
	AUTONOMIC NERVOUS SYSTEM	5	16	0.31
	BODY AS A WHOLE	20	16	1.25
	CENTRAL NERVOUS SYSTEM	3	16	0.19
	GASTROINTESTINAL	32	16	2.00
	HEART RATE/RHYTHM	6	16	0.38
	METABOLIC & NUTRITIONAL	3	16	0.19
	PSYCHIATRIC	6	16	0.38
	RED BLOOD CELL	5	16	0.31
	RESISTANCE MECHANISM	2	16	0.13
	RESPIRATORY	18	16	1.13
	SKIN AND APPENDAGES	5	16	0.31
	URINARY	2	16	0.13
	VASCULAR (EXTRACARDIAC)	2	16	0.13
	VISION	1	16	0.06

P20 STUDY

Data on chemistry scheme was supplied by the Applicant on the following patients in Study P20. Response data is taken from data discussed in the medical officer review of P20 in this MOR #2.

Pt. no.	Manufacturing scheme	RESPONSE
		R
		R
		R
		R
		R
		R

In this trial in completely-obstructing cancer, 3/7 responded with scheme and 3/5 responded with the NDA-directed scheme

Medical Officer Review #4 (Photofrin)

1.0 General Information:

1.1 NDA# 20-451
1.1.2 Review: M.O. Review #4
1.1.3 NDA Submission date: April 14, 1994
1.1.4 Date of Review May 17, 1995

1.2 Drug Name
1.2.1 Generic name: Sterile porfimer sodium
1.2.2 Trade name: Photofrin

1.3 Applicant: Quadralogic Technologies Inc.

1.4 Pharmacologic Category: Photosensitizer, antineoplastic agent

1.5 Proposed indication: Complete or partially obstructing esophageal cancer.

Subject of Review:

- Reviewer comments following Secondary Review of MOR #3.
- Comments regarding labeling, for communication to Applicant.
- Comments regarding Phase IV study to be required.

The proposed labeling suggests that patients can be treated with multiple courses of PDT. Recent discussions with Dr. Justice (secondary clinical Reviewer) and Dr. Felten (Device Reviewer) led to re-examination of data to see how often this had occurred in the submitted trials. The following table was prepared from the primary data, table 'VIIIC', the dosing table:

# of Patients Receiving 1, 2 or 3 courses of PDT

Study Protocol	1 course	2 courses	(% 2 courses)	3 courses	(% 3 courses)
19	110	42	38%	10	9%
20	17	8	47%	1	6%

About 40% of patients in Study 019 and about 50% in 020 received more than one course. Hence, a significant amount of the data reviewed in the NDA did involve patients receiving more than one course of therapy.

Adverse reaction data was tabulated from the AELIST table:

% Patients with an Adverse Reaction versus PDT course				
		Course Number of PDT		
		Course 1	Course 2	Course 3
Study P19	# PDT Patients	110	42	10
	% any ADR	87%	95%	90%
	% grade 3-4 ADR	40%	33%	30%
	% Grade 4 ADR	23%	12%	10%
Study P20	# PDT Patients	17	8	1
	% any ADR	94%	75%	
	% grade 3-4 ADR	59%	38%	
	% Grade 4 ADR	4%		

Obviously such an analysis is retrospective and subject to bias; however the existing evidence does not suggest an increase in overall adverse reactions, or serious (Grade 3-4) adverse reactions with second and 3rd courses of PDT. Since the wor' ,g of the draft labeling is similar to instructions givent to the investigators for performing the study, it seems reasonable to include the same wording in the labeling.

Requirement for Phase IV Study

During a meeting in January with Dr. Temple, it was noted that although the indication sought by ODAC included 'Patients with partially obstructing cancer of the esophagus who in the opinion of their Physicians are not candidates for YAG laser therapy', we have no prospective information on outcome in this group. Therefor it was suggested that we require a Phase IV study to collect data on safety and Dysphagia grade outcome in such patients.

Recommended Regulatory Action

The following comments on Labeling and Phase IV study should be sent to the Applicant by FAX transmission. Comments on labeling from Richard Felton regarding device issues should also be sent to the Applicant by FAX transmission. The applicant should resubmit draft labeling.

1. Labeling Comments

The following Clinical Comments regarding the labeling should be sent to the Applicant by FAX transmission along with the appendix of this review. 'Page #' below refers to page number in appendix of this review, which consists of copies of pages of Draft labeling with pertinent text underlined.

Page # **COMMENT**
(appendix)

(i) The asterisk for statistical significance should be removed. The column with Time to palliation failure should be removed. Either text or table should mention that the amount of missing data prohibited a statistical comparison of efficacy on the 2 arms.

Data on one-month dysphagia grade changes should be included as part of the efficacy presentation.

(ii) The indication should be "palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, should not be treated with ND-YAG laser therapy."

(iii) The underlined text in the warning section suggests testing skin for photosensitivity but gives no guidelines regarding when the test can be considered complete; such guidelines should be included in the labeling (and supported in an amendment).

(iv) Underlined text on combination studies in animals should be removed.

(vi) This statement regarding elderly patients is too dogmatic and should be removed. We don't have sufficient data to say safety and efficacy is equivalent in the young and the old.

(vii) The section on endobronchial carcinoma should be removed.

2. Phase IV study:

The recommended labeling includes a group of patients not formally evaluated in NDA studies:

"patients with partially obstructing esophageal cancer who, in the opinion of their physician, should not be treated with ND-YAG laser therapy."

As part of any approval package, the sponsor should agree to perform and should design a phase IV single-arm study to assess the efficacy (dysphagia response) and safety of PDT in this setting.

Grant A. Williams, M.D.

Robert T. Schultz, M.D.
5/17/95

cc: HFD 150 Gwilliams,PZimmerman x [redacted]
Application:NDA 20-451

Table 1

Course 1 Efficacy Results in the Randomized Trial

	Month 1 Improvement in Dysphagia (% of Pts.)	Month 1 Objective Tumor Response Rate (% of Pts.)	Median TPF† (Days)	Mean No. of Treatment Endoscopies Per Patient
PDT w/PHOTOFRIN (n=118)	35%	32%* (CR 2%, PR‡30%)	34	2.1
Nd:YAG (n=118)	29%	20% (CR 0%, PR‡20%)	42	2.8

*Statistically significant difference between PDT and Nd:YAG ($p < 0.05$)[1]

†Time to Palliation Failure

‡Based on esophageal luminal diameter

INDICATIONS AND USAGE

Photodynamic therapy with PHOTOFRIN is **indicated for the reduction of obstruction and palliation of dysphagia in patients with completely or partially obstructing esophageal cancer**[2]

WARNINGS

If the esophageal tumor is eroding into the trachea or bronchial tree, the likelihood of tracheoesophageal or bronchoesophageal fistula resulting from treatment is sufficiently high that PDT is not recommended.

All patients who receive PHOTOFRIN will be photosensitive and must observe precautions to avoid exposure of skin and eyes to direct sunlight or bright indoor light (from examination lamps, operating room lamps, etc.) for 30 days. **After 30 days, patients may expose a small area of skin (finger, dorsum of hand) to the sun for 5 minutes to test for residual photosensitivity. If significant erythema or blistering results,*** the patient should continue precautions against sun and bright light exposure for another 2 weeks before retesting the effects of limited sun exposure. UV sunscreens are of no value, because photoactivation is caused by visible light. Ocular discomfort, commonly described as sensitivity to sun, bright lights, or car headlights, has been reported in patients who received PHOTOFRIN. For 30 days, when outdoors, patients should wear dark sunglasses which have an average white light transmittance of < 4%. The patient should not be kept in a completely darkened room during this period, since photobleaching by exposure to low light levels may decrease the period of photosensitivity.

Drug Interactions

There is no documented clinical information concerning drug-drug interactions involving PHOTOFRIN. However, it is possible that concomitant use of other photosensitizing agents (e.g. tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemic agents, thiazide diuretics, and griseofulvin) would have the potential to increase the photosensitivity reaction.

Since the basic effects of PDT are thought to involve vasoconstriction and platelet activation and aggregation at the site of treatment, as well as the generation of active oxygen species, treatments which alter blood flow or availability of oxygen would be expected to have an effect on the effectiveness of PDT. Data from animal models and *in vitro* tissue culture studies suggest the following. Thromboxane A_2 receptor antagonists, thromboxane synthetase inhibitors, drugs which quench active oxygen species, and compounds which react with hydroxyl radicals, including dimethyl sulfoxide (DMSO), ethanol, formate, and mannitol, have been shown to decrease the effectiveness of PDT. Steroids administered 24-48 hours following PDT enhanced antitumor effects, whereas steroids administered concomitantly inhibited the PDT effect. **Animal or *in vitro* studies involving combination therapy with PDT and**

standard antineoplastic agents (including doxorubicin, mitomycin C, and BCG for bladder cancer, and mitomycin C in a colon cancer cell line) resulted in an increase in effectiveness compared with single therapies. Similarly, combinations of PDT with PHOTOFRIN and different photosensitizers with different biodistribution properties (including tetraphenylporphine sulfonate) resulted in enhanced tumor eradication in a murine mammary tumor model.*

Use in Elderly Patients

PDT with PHOTOFRIN is as safe and effective in elderly patients as in younger patients[3] The majority (79%) of patients treated with PDT using PHOTOFRIN in the clinical trials were at least 60 years of age. Dose modification based upon age is not required.

Endobronchial Carcinoma

Adverse events that occurred in >10% of patients with partially or completely obstructing endobronchial tumors treated with PDT using PHOTOFRIN included coughing, dyspnea, fever, hemoptysis, and pneumonia. In patients who received PDT followed by x-ray therapy, chest pain, dysphagia, nausea, pulmonary fibrosis, and radiation dermatitis were also seen at a frequency of >10%. Specific adverse events that occurred at statistically higher rates with PDT compared with control therapies were bronchitis and dyspnea. Potentially serious adverse events included bronchospasm, cardiac arrhythmias, myocardial infarction, pericardial effusion, fatal massive hemoptysis (prior x-ray therapy increases the risk of this), pneumothorax, respiratory insufficiency, weight decrease, pulmonary edema, pulmonary abscess, pulmonary embolism, pulmonary thrombosis, and stridor. The association of some of these adverse events with PDT with PHOTOFRIN is uncertain.[4]

Medical Officer Review of Safety Update

NDA 20-451 **December 18, 1995**
Drug: Photofrin

Regarding: Safety Update

Document Date 12-4-95

The safety update submitted August 4, 1995 covered about 1500 patients studied for various indications. This safety update includes information from an additional 268 patients evaluated in investigator studies or during emergency use which cross-referenced the QLT IND. The distribution of patients in the 2 safety updates is demonstrated in attached Table 1 from the submission.

Review of the data shows the adverse events to be similar to those reported in the original submission: events related to photosensitivity or to local reactions to the combination of light and photosensitizer.

Recommended Action: No action indicated.

Grant A. Williams, MD

JR Johnson, MD
12-18-95

cc: NDA 20-451; HFD-150: PZimmerman, G Williams
Division File

TABLE 1. Overview of Number of Patients Summarized

Study Number/Use	Study Design	Location	Number of Patients: August 1994 4-month Update PDT	August 1994 4-month Update Control	November 1995 Safety Update[a] PDT	November 1995 Safety Update[a] Control	Status
Study P626	Phase III esophageal: PDT vs Nd:YAG	Spain 1 center	5	5	–	–	Study closed January 1995; report scheduled for 1996.
Study P504	Phase III lung: PDT + XRT vs XRT alone vs EBT + XRT	Netherlands 1 center	12	24	–	–	Study closed November 1994; report scheduled for 1996.
Study P24	Phase II bladder: PDT only	US + Canada 15 centers	32	–	38	–	Study active. Last two patients enrolled in September 1995.
Emergency use	PDT in esophageal cancer	Canada 1 center	59	–	100	–	PHOTOFRIN® marketed in Canada for esophageal cancer September 1995. No longer available for emergency use.
Emergency use	PDT in various other oncologic indications	Canada many centers	42	–	58	–	N/A
Emergency use	PDT in various oncologic indications	US many centers	129	–	168	–	N/A
Investigator-sponsored studies	Phase I or II studies of PDT in various indications, usually without controls	US many centers	1,171	–	1,337	–	N/A

[a] As at August 31, 1995 for QLT studies, October 31, 1995 for emergency use patients, and July 31, 1995 for investigator-sponsored studies.

PDT = Photodynamic therapy with PHOTOFRIN®
XRT = External beam radiation
EBT = Endobronchial brachytherapy

EXCLUSIVITY SUMMARY FOR NDA # 20-451 SUPPL # ——

Trade Name PHOTOFRIN Generic Name PORFIMER SODIUM

Applicant Name QLT Phototherapeutics Inc. HFD # 150

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /✓/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength and route of administration, previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

~~(c) If the answers to (b)(1) and (b)(2) were both "no,"~~ identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain: _____

! _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature
Title: CSO

Date 7/5/95

Signature of Office/
Division Director

Date 7/12/95

cc: Original NDA Division File HFD-84

PATENT CERTIFICATION

NDA NUMBER: 20-451

Applicant: QLT Phototherapeutics Inc.*
c/o Bogle and Gates
Two Union Square
601 Union Street
Seattle, WA 98101-2346

* a U.S. subsidiary of Quadra Logic Technologies Inc.
520 West 6th Avenue
Vancouver, British Columbia
Canada V5Z 4H5

Active Ingredient: Porfimer Sodium

Certification: The undersigned certifies, based on her information, advice and belief that the above mentioned active ingredient, porfimer sodium, is the subject of composition claims in U.S. Patents Number 5,028,621; Number 4,866,168 and Number 4,649,151 all of which expire 10 March 2004, all assigned to Health Research Inc. In addition, methods to use porfimer sodium in photodynamic therapeutic protocols for tumor treatment are claimed in U.S. Patents Number 5,145,863 and Number 4,932,934 both of which expire 12 June 2007 and both assigned to Health Research, Inc. The Applicant has a valid and exclusive license to the above-mentioned patent from Health Research Inc.

Respectfully submitted,

Date 3/28/94

Kate H. Murashige
Morrison & Foerster
Attorney for QLT Phototherapeutics, Inc.
Registration No. 29,959

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-451 Trade (generic) names Photofrin, Porfimer Sodium

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ (4.) Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

This Indication - Esophageal Cancer

↳ Esophageal cancer is virtually non-existent in children.

There is some potential for use of photofrin / photodynamic therapy in other conditions that affect children and adults (e.g. laryngeal papillomatosis). For the presently-sought indications, however, pediatric studies do not need to be encouraged and would be virtually impossible to perform, given the rarity of esophageal cancer in childhood.

Robert J. DeAyala
Signature of Preparer

12/26/95
Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

Stat

Statistical Review and Evaluation

NDA#: 20-451

Title: A RANDOMIZED, PHASE III COMPARATIVE STUDY OF THE SAFETY AND EFFICACY OF PHOTODYNAMIC THERAPY (PDT) UTILIZING PHOTOFRIN II (DIHEMATOPORPHYRIN ETHERS [DHE])

versus

THERMAL ABLATION THERAPY USING THE Nd:YAG LASER FOR PARTIALLY OBSTRUCTING ESOPHAGEAL CARCINOMA.

Applicant: QLT Phototherapeutics INC

Name of Drug: Photofrin

Indication: treatment of biopsy-proven partially obstructing esophageal carcinoma.

Documents Reviewed: Volumes 1, 78, 79, 80, 85, 86, 87 from the original submission dated April 14, 1994 and Amendment dated may 16, 1994.

Medical Officer: Grant Williams

RELEVANT STATISTICAL ISSUES:

1) Changes in the average dysphagia grade from baseline at both Week 1 and Month 1 within each treatment group were not prospectively defined in the protocol. An average of one grade improvement in dysphagia from baseline within each treatment group at both Week 1 and Month 1 was used by the sponsor retrospectively, for the statistical significance of the "symptom palliation" endpoint within groups.

2) The magnitude of the difference in the average dysphagia grade at both Week 1 and Month 1 between the two treatment groups was not prospectively defined in the protocol for clinical significance.

3) The change in Esophageal Luminal Diameter was not prospectively defined in the protocol as an endpoint.

4) There was not any well designed statistical analysis comparing the efficacy of the new PHOTOFRIN lyophilized formulation versus the initially used frozen formulation.

1) BACKGROUND:

In this NDA the sponsor seeks approval for Photofrin in treating patients with biopsy-proven partially obstructing esophageal carcinoma. Eligible patients must be too debilitated

for, or have refused, or have failed to respond to, or had their cancers recurred following chemotherapy, radiation therapy or surgery. Patients must have not received prior therapy with either PDT or Nd:YAG laser and have not been treated with either chemotherapy or radiation within four weeks prior to randomization. This submission contains two reports: one controlled large study (P-19) that this review will focus on, and one uncontrolled small study (P-20) for treating patients with complete obstructing esophageal carcinoma.

II) DESCRIPTION OF STUDIES:

(a) Study P-19:

STUDY DESIGN: This is an open-label, randomized, multicenter, two arm Phase III trial designed to compare the efficacy and safety of (PDT) using PHOTOFRIN II dihematoporphyrin ethers (DHE) versus thermal ablation therapy using the Neodymium Yttrium-aluminum-garnet (Nd:YAD) laser for partially obstructing esophageal carcinoma. Patients randomized to receive PDT will first receive 2 mg/kg PHOTOFRIN II administered IV, followed 40-50 hours later by treatment with laser light of 630 nm from a continuous wave argon-ion pumped dye laser. The patient could receive up to a maximum of three PHOTOFRIN II injections, at least 30 days apart, and up to six laser light treatments, a maximum of two following each PHOTOFRIN II injection if necessary. Patients randomized to receive Nd:YAG laser therapy were treated with a laser power setting of between 15-90 W with a pulse duration of .5-4 seconds per pulse. Following each course of therapy patients were assessed for efficacy and safety at 1 week and 1, 2, 3 and 6 months after completion of treatment.

The study was not blinded to either the Investigator or the medical research staff, because both therapies have distinct differences in procedures. In addition, PDT therapy has an expected side effect of photosensitivity in approximately 20-40% of patients.

Patients were stratified by the presence of lesions $\geq$ 10 cm in length and whether they had received prior therapy. Eligible patients were randomized within strata balanced by center to receive either PDA or Nd:YAG using a computerized schema with a blocking factor of 4.

236 patients, 118 per treatment group were randomized between September 16, 1988, to July 16, 1992, in 24 centers.

The major efficacy endpoints were:

a) Symptom palliation, defined as change in dysphagia grade relative to the baseline dysphagia grade,

b) Time to treatment failure (TTF) as measured from the date of randomization (or date of start of therapy for second course) until the first occurrence of any of the following: worsening of dysphagia, therapeutic failure, disease progression, termination due to

treatment-related toxicities, death, request for withdrawal, protocol violation,

c) Time to palliation failure (TPF) defined as the interval from randomization (or date of start of therapy for second course) until the first evidence of lack of symptom palliation, worsening of dysphagia, or toxicity,

d) Objective tumor response.

The secondary efficacy endpoints were:

a) The change in Karnofsky performance status, b) the change in patient weight, c)survival, defined as the interval from randomization to death.

Baseline patient evaluations were required prior to randomization. Dysphagia was assessed at baseline and at all follow-up visits. It was graded on a 5 point scale as follows:

Grade	Description
1	Able to swallow all solids without difficulty. Asymptomatic.
2	Difficulty swallowing some hard solids, but able to swallow semisolids (blenderized or pureed foods).
3	Unable to swallow any solids; able to swallow liquids without any difficulty.
4	Difficulty in swallowing liquids.
5	Unable to swallow anything, including saliva.

A formal interim analysis of safety and efficacy was performed at the midpoint of the trial after the first 115 patients had achieved a minimum follow-up of 1 month. The primary indicator of effectiveness at the interim analysis was specified to be a prolongation of the time to treatment failure (TTF). The interim analysis was performed on the TTF data from these first 115 randomized patients. The logrank chi-square statistic was used to test for differences between the two treatment groups with respect to the distribution of TTF. Adjustment for the two analyses, interim and final, was based on the O'Brien-Fleming Procedure. For the interim analysis, a significance level of 0.005 was used. The significance level at the final analysis (based on the logrank statistic) was 0.048. Confidence intervals were adjusted based on these boundaries.

b) Other Studies: P-20. This is a multicenter, single-arm study designed to evaluate the safety and effectiveness of PDT in the palliative treatment of patients with completely obstructing esophageal carcinoma for whom no other acceptable option exists for palliation. 19 patients were enrolled out of 25 patients targeted in the protocol, from April 13, 1989 through August 25, 1992. 17 patients received treatment with PDT. This uncontrolled study will not be discussed.

III) EFFICACY RESULTS AND REVIEWER'S COMMENTS (Study P-19):

NOTE: Sponsor's Table series 12A - 12W referenced in this section were included in volume 85. The rest of the tables referenced in this section were included in volume 87. All these tables are included at the end of this report.

Symptom Palliation

The average dysphagia grades and average changes from baseline for both treatment groups are presented in sponsor's Table 12A for all available patients (sponsor's Table 12A.1 for evaluable patients). The average baseline dysphagia grade was approximately 3 for both treatment groups. Average change in dysphagia was similar for the two treatment groups at both Week 1 and Month 1, resulting in an approximately one grade improvement in dysphagia for the two treatment groups. The confidence interval for the average change between the two groups included zero indicating no statistically significant difference at either Week 1 or Month 1.

The Week 1 and Month 1 dysphagia scores (intent to treat analysis) are summarized as the distribution of patients who improved by at least one dysphagia grade relative to baseline (sponsor's Table 13). The distributions of the treatment groups were comparable with respect to improved patients at Week 1 and Month 1. Approximately 55% (65/118 PDT, 64/118 Nd:YAG) of patients in both treatment groups had at least one visit with an improved dysphagia grade. Approximately 31% (38/118 PDT, 35/118 Nd:YAG) of patients showed no evidence of improvement. Approximately 14% (15/118 PDT, 19/118 Nd:YAG) of patients were not evaluated. Approximately 23% (28/118 PDT, 27/118 Nd:YAG) of the patients had improved grades at both Week 1 and Month 1.

Sponsor's Table 12C displays the distribution of patients with improved dysphagia grades by baseline dysphagia grade. At the Week 1 visit, among patients with baseline dysphagia grades of 2, more Nd:YAG patients improved (17% 9/52 PDT, 33% 16/49 Nd:YAG), but among patients with a baseline dysphagia grade of 4, more PDT patients improved (75% 24/32 PDT, 65% 26/40 Nd:YAG). (The interpretation of the latter trend is complicated by a larger proportion of missing assessments within the Nd:YAG group (16% 5/32 PDT, 23% 9/40 Nd:YAG).) The proportion of patients with a baseline dysphagia grade of 3 who improved were 61% (17/28) for the PDT group and 57% (13/23) for the Nd:YAG group. The PDT group shows consistent, though small, improvements over all baseline grades at both Month 1 and Week 1.

Sponsor's tables 14-19 show the distribution of the changes in dysphagia grades from baseline to both Week 1 and Month 1.

Time to Treatment Failure

The distributions of TTF were similar for the two treatment groups. The median TTF was

35 days for PDT and 40 days for Nd:YAG B (sponsor's Table 12I). Kaplan-Meier plots of TTF for the first treatment course are presented in sponsor's figure 2 for both treatment groups. The estimated relative risk (=.99) was close to 1 which indicates that the risk of treatment failure is similar for the treatment groups. The 95% confidence interval for the relative risk ranged from (relative risk < 1 would indicate that treatment failure is more likely in PDT group). Since the confidence interval includes 1.0, this difference is statistically non significant.

Approximately 93% of the patients in each treatment arm have failed. Of the 15 patients who were censored (8 on PDT and 7 on Nd:YAG), none are still on study.

The predominate reasons for failure in the PDT arm were: worsening dysphagia (22%, 26/118), progressive disease (17%, 20/118), death (15%, 18/118) and dilatation performed (14%, 16/118). The predominate reasons for failure in the Nd:YAG arm were progressive disease (19%, 23/118), worsening dysphagia (19%, 22/118) and patient request (14%, 17/118).

Time to Palliation Failure

Time to palliation failure (TPF) was defined as the interval from randomization until the first evidence of: worsening dysphagia, treatment related toxicity, failure to palliate, retreatment or dilatation after Week 1 (sponsor's Table 12J). During the first course of treatment, 80% (94/118) of PDT patients and 70% (83/118) of Nd:YAG patients failed. In both treatment groups the most common reasons for failure were worsening dysphagia after Week 1 (26% 31/118 PDT, 26% 31/118 Nd:YAG), failure to palliate (24% 28/118 PDT, 25% 29/118 Nd:YAG), and retreatment or dilatation after Week 1 (17% 20/118 PDT, 12% 14/118 Nd:YAG).

The median TPF was longer for Nd:YAG patients than for PDT patients (34 days PDT, 42 days Nd:YAG). The hazard ratio (0.82) was less than 1 which suggests that PDT patients were more at risk of failure. The 95% confidence interval for the relative risk ranged from Since the confidence interval includes 1.0, this difference is statistically non significant.

Objective Response

Sponsor's Table 12K summarizes the distribution of objective response for all available assessments (intent-to-treat analysis) for the Week 1 and Month 1 visits of the first course (sponsor's Table 12K.1 for all evaluable data). There were few complete responses (2 PDT, 1 Nd:YAG) and none that lasted beyond the Month 1 visit. The response rates (CR+PR) of the treatment groups at the Week 1 visit were 45% (53/118) for the PDT group and 40% (47/118) for the Nd:YAG group. The difference of the response rates between the two treatment groups was statistically non significant. These rates declined for both treatment groups by the Month 1 visit; however, PDT patients had a higher response rate than did

Nd:YAG patients (32% 38/118 PDT, 20% 24/118 Nd:YAG) which was statistically significant. However, in the assessment of the overall responce rate, there are a large number of missing evaluations, particularly for the Nd:YAG treated patients. This is also pointed out by the sponsor.

Changes in Esophageal Lumen Diameters (This endpoint was not prospectively defined in the protocol).
Sponsor's Tables 28 and 29 summarize the effects of PDT and Nd:YAG therapy on esophageal luminal diameters following one course of therapy for the intent to treat and evaluable patient population respectively.

With respect to smallest luminal diameter measurements, both therapies produced changes (within treatment groups) from a baseline of 0.6 cm with increases of approximately 0.4 cm at Week 1 to 0.2 cm at Month 1. Since the confidence intervals do not include 0, these within group differences from baseline were statistically significant. The confidence interval for the between groups difference includes 0 (this difference is statistically non significant).

Therefore, PDT is effective in opening the lumen in patients with complete or partial obstructions.

The pattern of change in luminal diameters was similar in the evaluable population (Table 29).

KPS

Sponsor's Table 12Q presents the average change in KPS over time for the first course of treatment. The average baseline KPS scores of the two treatment groups were similar (78% PDT, 75% Nd:YAG). Both treatment groups had similar, small average decreases in KPS at the Week 1, Month 1, and Month 2 evaluations. During this time period, the average KPS scores fluctuated by less than 7%. After Month 2, there were too few patients remaining on study to provide a meaningful assessment.

Symptom Palliation (second course)

The second course averages of dysphagia grades and changes from baseline for each treatment group over time are presented in sponsor's Table 12S for all available grades, and Table 12S.1 for all evaluable data. The average baseline dysphagia grades were similar for the treatment groups at second course (2.50 PDT, 2.40 Nd:YAG). The average change from baseline also was similar for the treatment groups at the Week 1 and Month 1 visits. Dysphagia grade improved on average approximately 0.5 of a grade at Week 1 and showed little change relative to baseline at Month 1. Visits subsequent to Month 1 have too few patients to draw conclusions.

Time to Treatment Failure (second course)

Summary results for time to treatment failure (TTF) are presented in sponsor's Table 12T. Kaplan-Meier plots are presented in sponsor's Figure 3 for both treatment groups. The distributions of TTF were similar for the two treatment groups. The median TTF was 36 days for PDT patients and 35 days for Nd:YAG patients. The estimated relative risk of one (1.00) indicates that the risk of treatment failure is similar for the treatment groups. The 95% confidence interval for the relative risk ranged from (relative risk < 1 would indicate that treatment failure is more likely in PDT group). Ninety-three percent (93%) of PDT patients and 89% of Nd:YAG patients have failed. Of the 8 patients who were censored (3 PDT, and 5 Nd:YAG) none are still on study.

The predominant reasons for failure among PDT patients were worsening dysphagia (26%), dilatation (17%) and death (14%). Among Nd:YAG patients, patient request (21%) and progressive disease (19%) were the predominant reasons for failure.

Time to Palliation Failure (second course)

Time to palliation failure for the second course was defined as the interval from the start of treatment for the second course (date of injection for PDT patients, date of first laser for Nd:YAG patients) until the first evidence of: worsening dysphagia, treatment related toxicity, failure to palliate, retreatment or dilatation after Week 1 (sponsor's Table 12U).

During the second course of treatment 76% (32/42) of PDT patients and 70% (33/47) Nd:YAG patients failed. Among PDT patients the most common reasons for failure were worsening dysphagia after Week 1 and failure to palliate. Among Nd:YAG patients the most common reason for failure was failure to palliate. The median TPF was similar for the two treatment groups (33 days PDT vs 31 days Nd:YAG). The hazard ratio was approximately 1 (1.01), indicating that the risk of failure was similar for both groups. The 95% confidence interval for the relative risk ranged from 0.61 to 1.65.

Objective Response (second course)

The distribution of objective response rates for each treatment group at the Week 1 and Month 1 visits of the second course is presented in sponsor's Table 12V for all available assessments (sponsor's Table 12V.1 for all evaluable assessments). The response rate was higher for the PDT patients than for Nd:YAG patients at the Week 1 visit (45% 19/42 PDT, 30% 14/47 Nd:YAG) but statistically non significant. The Week 1 response rates based on evaluable assessments, which excludes missing assessments, were 64% for the PDT group and 61% for the Nd:YAG group. The difference of the response rates between the two treatment groups was statistically non significant. The treatment groups response rates at the Month 1 visit were 24% (10/42) for the PDT group and 19% (9/47) for the Nd:YAG group. The difference of the response rates between the two treatment groups was statistically non significant. Two PDT patients had a complete response at the Week 1 visit.

One of those patients and one additional PDT patient had a complete response at Month 1.

KPS (second course)

The mean KPS scores and the average change from baseline over time for each treatment group during the second course are displayed in Table 12W. The average KPS scores of both treatment groups were similar at baseline (79% PDT, 78% Nd:YAG) and at the Week 1 (76% PDT, 76% Nd:YAG) and Month 1 (76% PDT, 73% Nd:YAG) visits. The average KPS scores of either treatment group decreased by less than 7% at the Week 1 and Month 1 visits.

Change in Esophageal Luminal Diameter (Course 2) (This endpoint was not prospectively defined in the protocol).
Sponsor's Tables 38 and 39 present esophageal luminal diameter changes from baseline for Course 2 evaluations in those subsets of patients who received a second course of PDT or Nd:YAG treatment. In PDT-treated patients, the mean change in luminal diameter from baseline was an increase of 0.3 cm at Week 1, an increase of 0.2 cm at Month 1, and no change from baseline at Month 2. Results were similar to those patients treated with Nd:YAG. Adjusted (for interim analysis) confidence intervals include 0 indicating treatment changes are statistically non significant between the two treatment groups.

The change in esophageal lumen diameter was similar using the All Available and All Evaluable data subsets.

Survival

Summary results for survival are presented in sponsor's Table 12Y. The Kaplan-Meier estimate for the survival distribution is depicted in sponsor's Figure 4 for both treatment groups.

The survival distributions were similar for the two treatment groups. The median survival was similar for both groups; 123 days for PDT and 140 days for Nd:YAG. The estimated relative risk of 0.97 indicates that the risk of death is similar for the treatment groups. The 95% confidence interval for the relative risk ranged from (relative risk < 1 would indicate that PDT patients are more at risk for death).

Approximately 86% of the patients in each treatment arm have died. Of the 32 patients who were censored, 12 (4 PDT, 8 Nd:YAG) were known to be alive at the last follow-up (June 1993) while the remaining 20 patients (11 PDT, 9 Nd:YAG) were lost to follow-up.

EFFICACY ANALYSIS BY PHOTOFRIN FORMULATION

Sponsor's Tables 56 and 57 present dysphagia grade and objective tumor response analyses, respectively, by PHOTOFRIN formulation (frozen versus lyophilized). According to the sponsor, the frozen formulation was used at the beginning of the two trials and was replaced by the lyophilized form after about 40% of the patients had been enrolled. The majority of patients in both studies were therefore treated with the lyophilized formulation of PHOTOFRIN. According to the sponsor, comparisons between these two formulation groups are suspect because the patients were not randomly assigned. According to the sponsor, other contributing factors such as changing patient characteristics, the experience level of investigators (both existing and new), and changing device technology during the course of the studies may contribute to any observed differences.

The average improvement (about one grade for the frozen formulation and about half of a grade for the lyophilized formulation) in dysphagia grade from baseline within each formulation was statistically significant at both Week 1 and Month 1. The difference between the average improvements in dysphagia of both formulations was statistically significant at Week 1 in favor of the frozen formulation and statistically non significant at Month 1.

Patients treated with the lyophilized formulation of PHOTOFRIN had a high incidence of treatment related adverse experiences.

The Week 1 and the Month 1 differences of the objective response rates based on all available patients were statistically non significant between the two formulations.

CLINICAL ADVERSE EXPERIENCES:

Sponsor's Table 131 gives the proportion of patients with treatment related adverse experiences by treatment group. The proportion of patients with at least one adverse experience considered by the Investigator was 66% (73/110) for the PDT group and 37% (40/108) for the Nd:YAG group. The difference of these proportions between the two treatment groups is statistically significant in favor (fewer adverse experiences) of the Nd:YAG group.

The Medical Officer's review will include a more detailed discussion about the safety of the data.

SUMMARY AND CONCLUSIONS:

1) Symptom Palliation: During the first course of therapy, the average improvement (about 3/4 of a grade to 1 grade) in dysphagia grade from baseline within each treatment group was

was statistically significant at both Week 1 and Month 1.

The difference between the average improvements in dysphagia of both treatment groups was not statistically significant at either Week 1 or Month 1.

The same patterns hold for the second course therapy for Week 1 only for about an average improvement of a half grade.

2) Time to Treatment Failure: For either course of therapy, there was not any statistically significant difference between the two treatment groups in the Time to Treatment Failure.

3) Time to Palliation Failure: For either course of therapy, there was not any statistically significant difference between the two treatment groups in the Time to Palliation Failure.

4) Objective Response: During the first course of therapy, the objective response rate was higher, but not statistically significant, for the PDT patients (45%) than for Nd:YAG patients (40%) at the Week 1 visit based on all available assessments. The objective response rate was statistically significantly higher for the PDT patients (32%) than for Nd:YAG patients (20%) at the Month 1 visit based on all available assessments. The Week 1 and the Month 1 objective response rates based on evaluable assessments, which excludes missing assessments, were not statistically significantly different between the two treatment groups.

For the second course of therapy, the Week 1 and the Month 1 objective response rates based on either all the available assessments or the evaluable assessments, were not statistically significantly different between the two treatment groups.

5) KPS: During the first course of therapy, the average KPS scores of both treatment groups were similar at baseline and at the Week 1 and Month 1 visits. The average KPS scores within a treatment group decreased by less than 7% at the Week 1 and Month 1 visits. This decrease was only statistically significant for the PDT group at Week 1.

During the second course of therapy, the average KPS scores of both treatment groups were similar at baseline, at the Week 1 and Month 1 visits. The average KPS scores of either treatment group decreased by less than 7% at the Week 1 and Month 1 visits. These decreases were only statistically significant for the PDT group at Week 1 and Month 1 and for the YAG group at Month 1.

The between group comparisons were not statistically significant at Week 1 or Month 1.

6) Change in Esophageal Luminal Diameter: During the first course of therapy, with respect to the luminal diameter measurements, both therapies produced statistically significant changes from baseline at Week 1 and Month 1 based on either all available assessments or the evaluable assessments. The Week 1 and the Month 1 between group comparisons were not statistically significant based on either all the available assessments or

the evaluable assessments.

During the second course of therapy, with respect to the luminal diameter measurements, both treatment groups produced statistically significant changes from baseline at Week 1 only. The Week 1 and the Month 1 between group differences in luminal diameter measurements were not statistically significant based on either all the available assessments or the evaluable assessments.

7) Survival: There was no statistically significant difference between the two treatment groups in Survival.

8) The average improvement (about one grade for the frozen formulation and about half of a grade for the lyophilized formulation) in dysphagia grade from baseline within each formulation was statistically significant at both Week 1 and Month 1. The difference between the average improvements in dysphagia of both formulations was statistically significant at Week 1 in favor of the frozen formulation and statistically non significant at Month 1. The Week 1 and the Month 1 objective response rates based on all available patients were statistically non significantly different between the two formulations .

Conclusion: Photodynamic therapy with PHOTOFRIN does not seem to be more effective than the Nd:YAG therapy. Comparisons that show statistical significance in favor of PDT (e.g. objective response rate) between the two treatment groups must be interpreted with some caution. There is a large number of missing data, particularly, in the assessment of the overall objective response rate. The safety of PDT for this indication must be of a concern. Patients treated with the lyophilized formulation of PHOTOFRIN had a high incidence of treatment related adverse experiences. There is some suggestion that the lyophilized formulation may be less effective than the frozen formulation.

Finally, statistical analyses involving the changes in the average dysphagia grade from baseline at both Week 1 and Month 1 within each treatment group should be given less weight, since the magnitude of the difference in the average dysphagia grade for clinical significance at both Week 1 and Month 1 between the two treatment groups and within each treatment group was not prospectively defined in the protocol.

Koutsoukos, A.

Antonis Koutsoukos, Ph.D.
Mathematical Statistician.

Concur: for Dr. Wilson 8/16/94

Dr. Dubey 8/16/94

cc: NDA #20-451
HFD-150
HFD-150/G. Burke, MD, PhD
HFD-150/J. Johnson, MD
HFD-150/P. Zimmerman, CSO
HFD-150/G. Williams MD
HFD/713/S. Dubey, PhD [File: DRU 1.3.2 NDA]
HFD/713/S. Wilson, PhD
HFD/713/C. Gnecco, PhD
HFD/713/A. Koutsoukos, PhD

Antonis Koutsoukos / 8-11-94 /WP6.0.a- c:\NDA1\photofri.rvw

This review consists of 12 pages of text and 30 pages of tables and figures.

Table 12A. Change From Baseline in Dysphagia Grade Over Time at First Course by Treatment Group

VISIT	All Available Grades			
	PDT		Nd:YAG	
	NO. PTS.	AVG. SCORE	NO. PTS.	AVG. SCORE
Baseline	118	2.86	118	2.89
Week 1	93	2.22	93	1.98
Change	93	-0.73	93	-0.90
95% C.I.				
Within Grp.[1]	(-0.98, -0.48)		(-1.13, -0.67)	
Between Grp.[2]	0.17 (-0.17, 0.51)			
Month 1	75	2.09	68	2.18
Change	75	-0.75	68	-0.68
95% C.I.				
Within Grp.[1]	(-1.02, -0.48)		(-0.93, -0.42)	
Between Grp.[2]	-0.07 (-0.45, 0.31)			
Month 2	28	2.61	20	2.30
Change	28	-0.11	20	-0.40
*				
Month 3	12	2.25	8	2.38
Change	12	0.00	8	0.13
*				
Month 6	5	2.20	4	1.50
Change	5	-0.20	4	-0.25
*				

1. 95% C.I. for within group mean change from baseline.
2. 95% C.I. for between group difference in mean changes from baseline. The O'Brien-Fleming method was used to adjust the width of the confidence interval [35].

* Confidence interval not calculated, too few patients to assess

References: Appendices IV, IX.A, IX.C

78A

Table 12A.1. Change From Baseline in Dysphagia Grade at First Course by Treatment Group

VISIT	Evaluable Grades PDT NO. PTS.	PDT AVG. SCORE	Nd:YAG NO. PTS.	Nd:YAG AVG. SCORE
Baseline	113	2.87	116	2.90
Week 1	87	2.17	89	1.89
Change	83	-0.80	87	-1.01
95% C.I. Within Grp.[1]	(-1.05, -0.54)		(-1.23, -0.80)	
Between Grp.[2]	0.22 (-0.12, 0.55)			
Month 1	74	2.09	63	2.11
Change	69	-0.75	61	-0.74
95% C.I. Within Grp.[1]	(-1.04, -0.46)		(1.01, -0.47)	
Between Grp.[2]	-0.02 (-0.42, 0.38)			
Month 2	26	2.58	20	2.30
Change	24	-0.13	20	-0.40
*				
Month 3	12	2.25	8	2.38
Change	10	0.00	8	0.13
*				
Month 6	4	2.00	4	1.50
Change	3	-0.00	4	-0.23

1. 95% C.I. for within group mean change from baseline.
2. 95% C.I. for between group difference in mean changes from baseline. The O'Brien-Fleming method was used to adjust the width of the confidence interval [35].

* Confidence interval not calculated too few patients to assess

References: Appendices IV, IX.A, IX.B

PHOTOF 94017001T1
03/15/94 (M11/AL5-29)

TABLE 13. Course 1 Response Assessments Based on Improvement in Dysphagia Grades

Intent-to-Treat Analysis

Response Category	Number (%) of Patients					
	P19				P20	
	PDT n=118		Nd:YAG n=118		PDT n=19	
RESPONDERS[a]						
Any assessment[b]	65	(55)	64	(54)	13	(68)
Week 1	52	(44)	57	(48)	12	(63)
Month 1	41	(35)	34	(29)	8	(42)
Week 1 and Month 1	28	(24)	27	(23)	7	(37)
NONRESPONDERS	38	(32)	35	(30)	4	(21)
NOT EVALUATED	15	(13)	19	(16)	2	(11)

[a] Patients with improved dysphagia grades
[b] Patients with improved response at Week 1 or Month 1

Table 12C. Summary of Improvement From Baseline in Dysphagia Grade at Week 1 and Month 1 Visits by Baseline Dysphagia Grade and Treatment Group

Baseline Dysphagia Grade TOTAL PTS.	Improved				Not Improved		Missing	
	PDT No. (%)	Nd:YAG No. (%)	PDT No. (%)	Nd:YAG No. (%)	PDT No. (%)	Nd:YAG No. (%)	PDT No. (%)	Nd:YAG No. (%)
Week 1								
1	2 (100)	4 (100)	+0 (0%)	+0 (0%)	1 (50%)	4 100%)	1 (50%)	0 (0%)
2	52 (100)	49 (100)	9 (17%)	16 (33%)	29 (56%)	22 (45%)	14 (27%)	11 (22%)
3	28 (100)	23 (100)	17 (61%)	13 (57%)	6 (21%)	5 (22%)	5 (18%)	5 (22%)
4	32 (100)	40 (100)	24 (75%)	26 (65%)	3 (9%)	5 (13%)	5 (16%)	9 (23%)
5	4 (100)	2 (100)	2 (50%)	2 (100%)	2 (50%)	0 (0%)	0 (0%)	0 (0%)
Month 1								
1	2 (100)	4 (100)	+0 (0%)	+0 (0%)	1 (50%)	4 (100%)	1 (50%)	0 (0%)
2	52 (100)	49 (100)	11 (21%)	7 (14%)	22 (42%)	20 (41%)	19 (37%)	22 (45%)
3	28 (100)	23 (100)	10 (36%)	7 (30%)	9 (32%)	5 (22%)	9 (32%)	11 (48%)
4	32 (100)	40 (100)	19 (59%)	20 (50%)	2 (6%)	5 (13%)	11 (34%)	15 (38%)
5	4 (100)	2 (100)	1 (25%)	0 (0%)	0 (0%)	0 (0%)	3 (75%)	2 (100%)

+Patients within a baseline dysphagia grade of 1 cannot show improvement

Reference: Appendices IV, IX.A, IX.B

PHOTOF 94017001T2 (M11/AM4-2)
03/15/94

TABLE 14. Week-1 Response Based on Improvement in Dysphagia Grades by Baseline Grade

All Available Data

Number[a]/Total[b] (%) of Patients

Baseline Dysphagia Grade	P19					P20	
	PDT		Nd:YAG		Difference[c] (PDT-Nd:YAG)	PDT	
1	0/2	(0)	0/4	(0)	(0)	0	(0)
2	9/52	(17)	16/49	(33)	(-16)	0	(0)
3	17/28	(61)	13/23	(57)	(4)	0	(0)
4	24/32	(75)	26/40	(65)	(10)	5/7	(71)
5	2/4	(50)	2/2	(100)	(-50)	7/12	(58)

[a] Number of patients who had an improvement in dysphagia grade
[b] Number of patients with specific dysphagia grade at baseline
[c] Difference in percentage response rates

TABLE 15. Month-1 Response Based on Improvement in Dysphagia Grades by Baseline Grade

All Available Data

Number[a]/Total[b] (%) of Patients

Baseline Dysphagia Grade	P19					P20	
	PDT		Nd:YAG		Difference[c] (PDT-Nd:YAG)	PDT	
1	0/2	(0)	0/4	(0)	(0)	0	(0)
2	11/52	(21)	7/49	(14)	(7)	0	(0)
3	10/28	(36)	7/23	(30)	(6)	0	(0)
4	19/32	(59)	20/40	(50)	(9)	2/7	(29)
5	1/4	(25)	0/2	(0)	(25)	6/12	(50)

[a] Number of patients who had an improvement in dysphagia grade
[b] Number of patients with specific dysphagia grade at baseline
[c] Difference in percentage response rates

TABLE 16. Baseline to Week-1 Change in Dysphagia Grades in Study P19 (PDT)

Baseline Dysphagia Grade	Change in Dysphagia Grade at Week 1 with PDT									
	Worsening in Dysphagia			No Change	Improvement in Dysphagia					
	3 Grades	2 Grades	1 Grade	0	1 Grade	2 Grades	3 Grades	4 Grades	Missing	Total
1	0	0	0	1	0	0	0	0	1	2
2	0	2	4	23	9	0	0	0	14	52
3	0	2	3	1	12	5	0	0	5	28
4	0	0	0	3	7	11	6	0	5	32
5	0	0	0	2	1	0	0	1	0	4
TOTAL	0	4	7	30	29	16	6	1	25	118

TABLE 17. Baseline to Week-1 Change in Dysphagia Grades in Study P19 (Nd:YAG)

Baseline Dysphagia Grade	Change in Dysphagia Grade at Week 1 with Nd:YAG									
	Worsening in Dysphagia			No Change	Improvement in Dysphagia					
	3 Grades	2 Grades	1 Grade	0	1 Grade	2 Grades	3 Grades	4 Grades	Missing	Total
1	0	0	0	4	0	0	0	0	0	4
2	0	1	1	20	16	0	0	0	11	49
3	0	1	1	3	7	6	0	0	5	23
4	0	0	2	3	7	13	6	0	9	40
5	0	0	0	0	0	1	0	1	0	2
TOTAL	0	2	4	30	30	20	6	1	25	118

TABLE 18. Baseline to Month-1 Change in Dysphagia Grades in Study P19 (PDT)

Baseline Dysphagia Grade	Change in Dysphagia Grade at Month 1 with PDT									
	Worsening in Dysphagia			No Change	Improvement in Dysphagia					
	3 Grades	2 Grades	1 Grade	0	1 Grade	2 Grades	3 Grades	4 Grades	Missing	Total
1	0	0	0	1	0	0	0	0	1	2
2	1	0	0	21	11	0	0	0	19	52
3	0	1	4	4	6	4	0	0	9	28
4	0	0	0	2	8	5	6	0	11	32
5	0	0	0	0	0	0	0	1	3	4
TOTAL	1	1	4	28	25	9	6	1	43	118

TABLE 19. Baseline to Month-1 Change in Dysphagia Grades in Study P19 (Nd:YAG)

Baseline Dysphagia Grade	Change in Dysphagia Grade at Month 1 with Nd:YAG									
	Worsening in Dysphagia			No Change	Improvement in Dysphagia					
	3 Grades	2 Grades	1 Grade	0	1 Grade	2 Grades	3 Grades	4 Grades	Missing	Total
1	0	1	1	2	0	0	0	0	0	4
2	0	0	2	18	7	0	0	0	22	49
3	0	0	2	3	4	3	0	0	11	23
4	0	0	1	4	6	11	3	0	15	40
5	0	0	0	0	0	0	0	0	2	2
TOTAL	0	1	6	27	17	14	3	0	50	118

Table 12I. Summary of Time to Treatment Failure For All Patients by Treatment Group

	PDT NO. PTS.	(%)	Nd:YAG NO. PTS.	(%)
Randomized	118	100.0	118	100.0
Number Failures/Reason	110	93.2	111	94.1
Progressive disease	20		23	
Worsening dysphagia	26		22	
Dilatation	16		10	
Retreatment	9		10	
Treatment-related term	6		5	
Death (any cause)	18		11	
Pt. request/Pt. failure	10		17	
Patient deterioration	5		13	
Number Censored/Reason	8	6.8	7	5.9
Non-treatment related term.	8		7	
Median TTF (days) [95% CI]	35 [34, 40]		40 [33, 42]	
Range	(0-211)		(0-183)	
Wilcoxon Chi-square (1 df)/p-value	0.008/0.9268			
Mantel-Cox Chi-square (1 df)/p-value	0.012/0.9140			
Hazard Ratio (Nd:YAG/PDT)*	0.99			
[95% CI]	[0.76, 1.29]			

* BMDP2L with Treatment variable as covariate.

References: Appendices IV, IX.A, IX.B

PHOTOF 94017001T1
03/15/94 (M11/AL5-39)

D73P19

Figure 2. Time To Treatment Failure At First Treatment Course

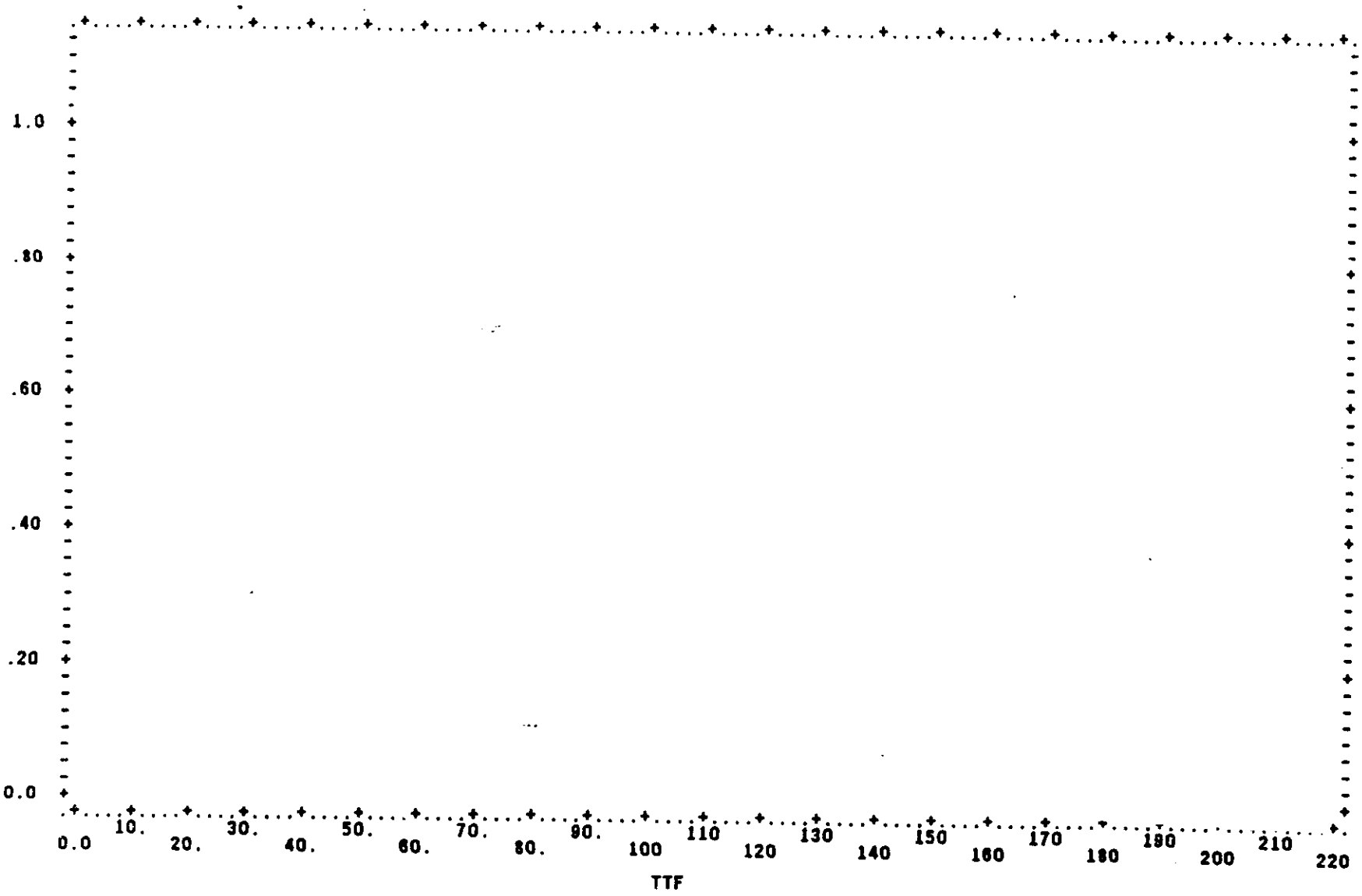


Table 12J. Summary of Time to Palliation Failure for All Randomized Patients in First Course by Treatment Group

	TREATMENT			
	PDT		Nd:YAG	
	NO.	(%)	NO.	(%)
Number Randomized: 236	118	(100)	118	(100)
Number Failures/Reason	94	(79.7)	83	(70.3)
Worsening dysphagia at 1 Week	10		4	
Worsening dysphagia at > Week 1	31		31	
Failure to palliate	28		29	
Termination - treatment related	5		5	
Death - treatment related	0		0	
Dilatation or retreatment > Week 1	20		14	
Number Censored/Reason	24	(20.3)	35	(29.7)
Censored reason (non-failures)	24		35	
Median TPF (days)[95% CI][a]	34	[31,37]	42	[33,45]
Range	(0-211)		(0-183)	
Wilcoxon Chi-square (1 df) /p-value	2.769 / 0.0961			
Mantel-Cox Chi-square (1 df) /p-value	1.889 / 0.1694			
Hazard Ratio (Nd:YAG/PDT)[b] 95% C.I.	0.82 [0.60, 1.10]			

a: Brookmyer - Crowly Method.
b: A Cox regression model with one term for treatment was used to calculate these estimates. This regression analysis was generated via SAS using PROC BMDP2L.

References: Appendices IV, IX.B, IX.D

PHOTOF 9401J001T1
03/15/94 (M11/AL5-40)

Table 12K. Distribution of Objective Response at Week 1 and Month 1 During the First Course by Treatment Group

VISIT/ GRADE	All Available Assessments PDT NO. PTS.	%	Nd:YAG NO. PTS.	%
Baseline	118	100	118	100
Week 1	118	100	118	100
CR1	2	1.7	1	0.9
CR2	0	0.0	0	0.0
PR	51	43.2	46	39.0
SD	28	23.7	26	22.0
PD	4	3.4	1	0.9
Missing	33	28.0	44	37.3
CR+PR (rate)[1]		44.9		39.8
(95% C.I.) Within Grp.[2]		(35.8, 53.3)		(30.9, 49.3)
Between Grp.[3]		5.09 (-7.61, 17.79)		
Month 1	118	100	118	100
CR1	1	0.9	0	0.00
CR2	1	0.9	0	0.00
CR3	0	0.00	0	0.00
PR	36	30.5	24	20.3
SD	18	15.3	17	14.4
PD	13	11.0	16	13.6
Missing	49	41.5	61	51.7
CR+PR (rate)[1]		32.2		20.3
(95% C.I.) Within Grp.[2]		(23.90, 41.43)		(13.49, 28.73)
Between Grp.[3]		11.86 (0.63, 23.09)		

1. Denominator for response rate=number of randomized patients
2. 95% confidence interval for treatment group response rate
3. 95% confidence interval for difference between response rates of the treatment groups (PDT-Nd:YAG). The O'Brien-Fleming method was used to adjust the width of the confidence interval.

References: Appendices IV, IX.E

PHOTOF 9401700IT1
03/15/94 (M11/AL5-41)

Table 12K.1. Distribution of Objective Response at Week 1 and Month 1 During the First Course by Treatment Group

VISIT/ GRADE	Evaluable Assessments PDT NO. PTS.	%	Nd:YAG NO. PTS.	%
No. Evaluable Patients	73	100	72	100
Week 1	73	100	72	100
CR1	2	2.7	1	1.4
CR2	0	0.0	0	0.0
PR	46	63.0	44	61.1
SD	23	31.5	26	36.1
PD	2	2.7	1	1.4
Missing/NE	45		46	
CR+PR (rate)[1]		65.8		62.5
(95% C.I.)				
Within Grp.[2]		(53.72, 76.47)		(50.30, 73.64)
Between Grp.[3]		3.25 (-12.49, 19.00)		
Month 1	68	100	57	100
CR1	1	1.5	0	0.00
CR2	1	1.5	0	0.00
PR	36	52.9	24	42.11
SD	17	25.0	17	29.82
PD	13	19.1	16	28.07
Missing/NE	50		61	
CR+PR (rate)[1]		55.9		42.1
(95% C.I.)				
Within Grp.[2]		(43.32, 67.92)		(29.14, 55.92)
Between Grp.[3]		13.77 (-3.81, 31.35)		

1. Denominator for response rate=number of patients with evaluable assessments.
2. 95% confidence interval for treatment group response rate
3. 95% confidence interval for difference between response rates of the treatment groups (PDT-Nd:YAG). The O'Brien-Fleming method was used to adjust the width of the confidence interval.

References: Appendices IV, IX.E

PHOTOF 94017001T1
03/15/94 (M11/AL5-42)

TABLE 28. Course 1 Luminal Diameters (cm) and Changes From Baseline
All Available Data

Visit	P19			P20
	PDT	Nd:YAG	Difference (PDT-Nd:YAG)	PDT
BASELINE				
Mean luminal diameter (n)[a]	0.66 (112)	0.60 (112)		0.10 (19)
WEEK 1				
Mean luminal diameter (n)[a]	1.05 (86)	1.05 (73)		0.67 (15)
Mean change (n)[b]	0.41 (85)	0.44 (73)	(-0.03)	0.60 (15)
[95% CI[c]-mean change]	[0.30, 0.52]	[0.35, 0.53]	[-0.17, 0.12]	[0.43, 0.77]
MONTH 1				
Mean luminal diameter (n)[a]	0.90 (67)	0.74 (58)		0.66 (9)
Mean change (n)[b]	0.27 (67)	0.18 (57)	(0.09)	0.60 (9)
[95% CI-mean change)	[0.16, 0.38]	[0.08, 0.27]	[-0.06, 0.24]	[0.30, 0.90]
MONTH 2				
Mean luminal diameter (n)[a]	0.86 (24)	0.92 (19)		0.65 (2)
Mean change (n)[b]	0.16 (24)	0.23 (19)	(-0.06)	0.64 (2)
[95% CI-mean change]	[0.01, 0.32]	[0.09, 0.36]	[-0.37, 0.28]	[d]

[a] (n) represents the number of patients with evaluable assessments at this visit.
[b] Negative changes indicate improvements from baseline, positive changes indicate worsening. (n) represents the number of patients with evaluable assessments both at this visit and at baseline.
[c] CI = Confidence Interval, adjusted using O'Brien-Fleming Procedure for the between-group comparison to reflect the interim analysis
[d] Too few patients

TABLE 29. Course 1 Luminal Diameters (cm) and Changes From Baseline

All Evaluable Data

Visit	P19			P20
	PDT	Nd:YAG	Difference (PDT-Nd:YAG)	PDT
BASELINE				
n	112	112		19
Mean luminal diameter	0.66	0.60		0.10
WEEK 1				
n	73	71		13
Mean luminal diameter	1.10	1.04		0.72
Mean change	0.49	0.43	0.06	0.66
[95% CI[a]-mean change]	[0.38, 0.60]	[0.33, 0.52]	[-0.08, 0.21]	[0.50, 0.83]
MONTH 1				
n	66	57		9
Mean luminal diameter	0.90	0.74		0.66
Mean change	0.28	0.18	(0.11)	0.60
[95% CI-mean change]	[0.17, 0.40]	[0.08, 0.27]	[-0.04, 0.26]	[0.30, 0.90]
MONTH 2				
n	24	19		2
Mean luminal diameter	0.86	0.92		0.65
Mean change	0.16	0.23	(-0.06)	0.64
[95% CI-mean change]	[0.01, 0.32]	[0.09, 0.36]	[-0.37, 0.28]	[b]

[a] CI = Confidence Interval, adjusted using O'Brien-Fleming Procedure for the between-group comparison to reflect the interim analysis

[b] Too few patients

Table 12Q. Change from Baseline in KPS Over Time at First Course by Treatment Group

	All Available Grades			
	PDT		Nd:YAG	
VISIT	NO. PTS.	AVG. SCORE	NO. PTS.	AVG. SCORE
Baseline	118	77.7	118	74.7
Week 1	96	74.4	91	73.0
Change	96	-4.2	91	-1.3
95% C.I.				
Within Group[1]	(-7.26, -1.07)		(-4.01, 1.60)	
Between Group[2]	-2.96 (-7.17, 1.26)			
Month 1	76	77.6	66	74.5
Change	76	-1.4	66	-2.3
95% C.I.				
Within Group[1]	(-5.52, 2.73)		(-5.73, 1.19)	
Between Group[2]	0.88 (-4.55, 6.31)			
Month 2	29	73.6	17	70.6
Change	29	-3.6	17	-6.5
*				
Month 3	12	70.8	7	80.0
Change	12	-9.2	7	1.4
*				
Month 6	5	82.0	3	83.3
Change	5	-2.0	3	3.3
*				

1. 95% C.I. for within group mean change from baseline.
2. 95% C.I. for between group difference in mean changes from baseline. The O'Brien-Fleming method was used to adjust the width of the confidence interval [35].

* Confidence interval not calculated too few patients to assess

References: Appendices IV, IX.F

87A

PHOTOF 94017001T1
03/15/94 (M11/AL5-53)

Table 12S. Change From Baseline Dysphagia Grade Over Time at Second Course by Treatment Group

	All Available Grades			
	PDT		Nd:YAG	
VISIT	NO. PTS.	AVG. SCORE	NO. PTS.	AVG. SCORE
Baseline	42	2.50	47	2.43
Week 1	38	2.18	28	1.79
Change	38	-0.39	28	-0.57
(95% C.I.) Within Grp.[1]	(-0.79, 0.00)		(-0.93, -0.22)	
Between Grp.[2]	0.18(-0.36, 0.71)			
Month 1	29	2.21	28	2.43
Change	29	-0.17	28	0.04
(95% C.I.) Within Grp.[1]	(-0.64, 0.29)		(-0.35, 0.42)	
Between Grp.[2]	-0.21 (-0.82, 0.40)			
Month 2	7	2.00	6	2.50
Change *	7	0.00	6	0.50
Month 3	2	2.50	0	
Change *	2	0.50	0	
Month 6	1	2.00	0	
Change	1	0.00	0	

1. 95% confidence interval for treatment group response rate.
2. 95% confidence interval for difference between response rates of the treatment groups (PDT - Nd:YAG). The O'Brien-Fleming method was used to adjust the width of the confidence interval [35].

* Confidence interval not calculated, too few patients to assess.

References: Appendices IV, IX.A, IX.C

88B

PHOTOF 94017001T1
03/15/94 (M11/AL5-56)

Table 12S.1. Change From Baseline in Dysphagia Grade Over Time At Second Course by Treatment Group.

	Evaluable Grades			
	PDT		Nd:YAG	
VISIT	NO. PTS.	AVG. SCORE	NO. PTS.	AVG. SCORE
Baseline	42	2.50	47	2.40
Week 1	36	2.19	28	1.79
Change	36	-0.42	28	-0.57
(95% C.I.)				
Within Grp.[1]	(-0.83, -0.01)		(-0.93, -0.22)	
Between Grp.[2]	0.20(-0.36, 0.76)			
Month 1	27	2.26	26	2.35
Change	27	-0.11	26	-0.04
(95% C.I.)				
Within Grp.[1]	(-0.61, 0.38)		(-0.37, 0.30)	
Between Grp.[2]	-0.07 (-0.68, 0.50)			
Month 2	7	2.00	5	2.40
Change	7	0.00	5	0.40
*				
Month 3	2	2.50	0	
Change	2	0.50	0	
*				
Month 6	1	2.00	0	
Change	1	0.00	0	

1. 95% confidence interval for treatment group response rate.
2. 95% confidence interval for difference between response rates of the treatment groups (PDT - Nd:YAG). The O'Brien-Fleming method was used to adjust the width of the confidence interval [35].

* Confidence not calculated, too few patients to assess.

References: Appendices IV, IX.A, IX.C

PHOTOF 94017001T1
03/15/94 (M11/AL5-55)

Table 12T. Summary of Time to Treatment Failure for All Patients by Treatment Group Second Course

	PDT NO. PTS.	PDT (%)	Nd:YAG NO. PTS.	Nd:YAG (%)
Number Retreated	42	100.0	47	100.0
Number Failures/Reason	39	92.9	42	89.4
Progressive disease	3		9	
Worsening dysphagia	11		2	
Dilatation	7		5	
Retreatment	2		2	
Treatment-related term	2		4	
Death (any cause)	6		4	
Pt request/Pt failure	4		10	
Patient deterioration	4		6	
Number Censored/Reason	3	7.1	5	10.6
Non-treatment related term	3		5	
Median TTF (days) [95% C.I.] Range	36[33, 40]		35[29, 41]	
Wilcoxon Chi-square (1 df)/p-value	0.286/0.5929			
Mantel-Cox Chi-square (1 df)/p-value	0.000/0.9959			
Hazard Ratio (Nd:YAG/PDT)[a]	1.00			
[95% CI][b]	(0.64, 1.56)			

[a] BMDP2L with Treatment variable as covariate.
[b] Adjusted for O'Brien-Fleming procedure

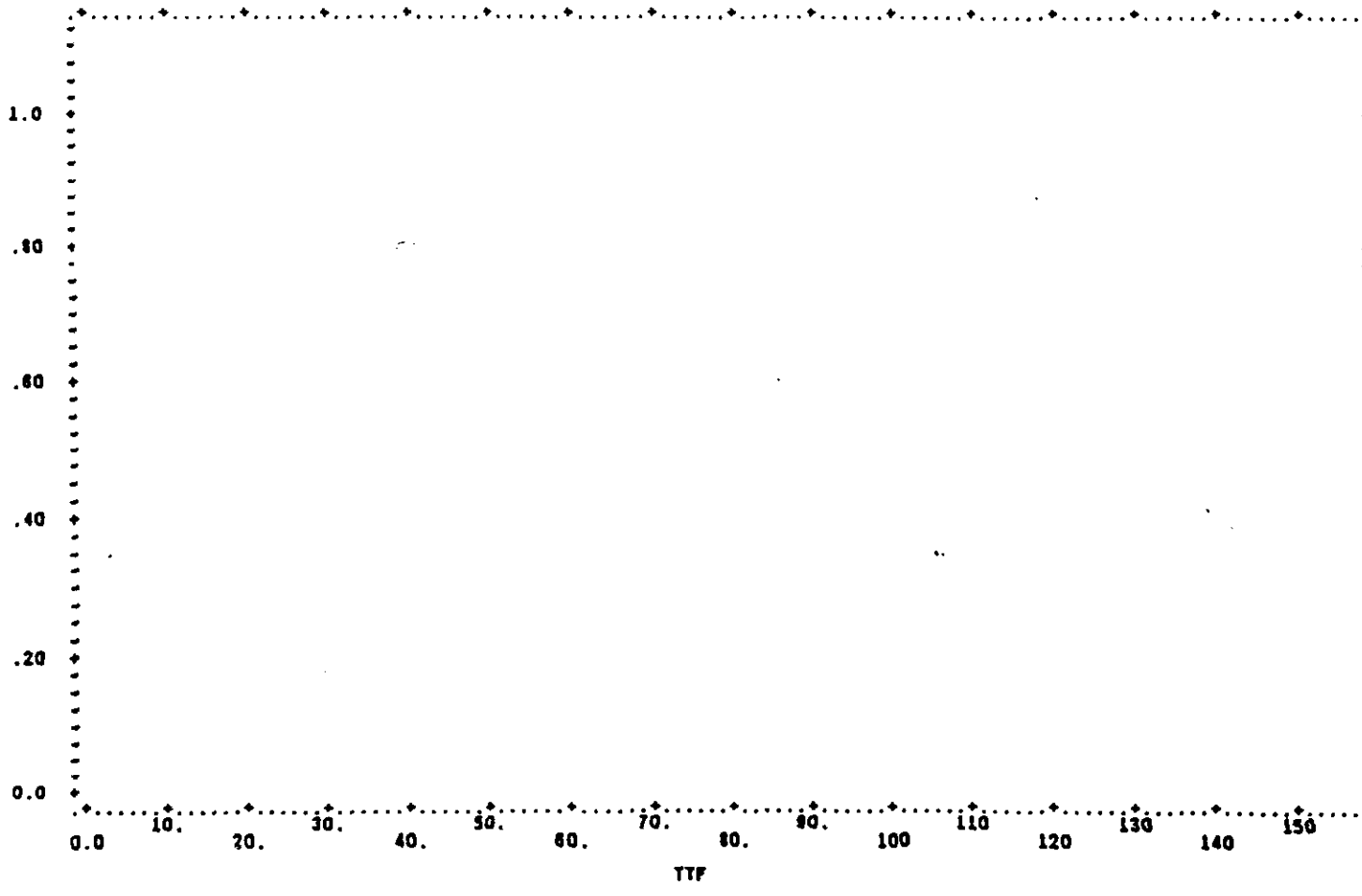
References: Appendices IV, IX.A, IX.C

89A

PHOTOF 94017001T1
03/15/94 (M11/AL5-57)

D73P19

Figure 3. Time To Treatment Failure At Second Course



P is PDT Y is YAG

Table 12U. Summary of Time to Palliation Failure for All Randomized Patients in Second Course by Treatment Group

	TREATMENT			
	PDT		Nd:YAG	
	NO. PTS.	(%)	NO. PTS.	(%)
Number Retreated	42	(100)	47	(100)
Number Failures	32	(76.2)	33	(70.2)
Worsening dysphagia at 1 Week	3		0	
Worsening dysphagia at > Week 1	14		7	
Failure to palliate	11		21	
Termination - treatment related	1		2	
Death - treatment related	1		0	
Dilatation or retreatment > Week 1	2		3	
Number Censored	10	(23.8)	14	(29.8)
Censored reason (non-failures)	10		14	
Median TPF [95% C.I.] (days)[a]	33	[10,38]	31	[10,35]
Range				
Wilcoxon Chi-square (1 df) /p-value	0.207 / 0.6494			
Mantel-Cox Chi-square (1 df) /p-value	0.001 / 0.9782			
Hazard Ratio (YAG:PDT)[b]	1.01			
95% C.I.[c]	[0.61, 1.65]			

*: Censored observation
a: Brookmyer-Crowley confidence interval from BMDP1L output.
b: A Cox regression model with one term for treatment was used to calculate these estimates. This regression analysis was generated via using PROC BMDP2L.
c: Adjusted by using O'Brien-Fleming procedure (1.977).

References: Appendices IV, IX.B, IX.D

9GA

PHOTOF 94017001T1
03/15/94 (M11/AL5-58)

Table 12V. Distribution of Objective Response at Week 1 and Month 1 During the Second Course by Treatment Group

VISIT	All Available Assessments PDT NO. PTS. %			Nd:YAG NO. PTS. %	
Randomized					
Week 1	42	100		47	100
CR1	1	2.4		0	0.0
CR2	0	0.0		0	0.0
CR3	1	2.4		0	0.0
PR	17	40.5		14	29.8
SD	10	23.8		9	19.1
PD	0	0.0		0	0.0
Missing	13	31.0		24	51.0
CR+PR (rate)[1]		45.2			29.8
(95% C.I.)					
Within Grp.[2]		(29.9, 61.3)			(17.3, 44.9)
Between Grp.[3]			15.5(-4.7, 35.6)		
Month 1	42	100		47	100
CR1	2	4.8		0	0.0
CR2	0	0.0		0	0.0
CR3	0	0.0		0	0.0
PR	8	19.0		9	19.1
SD	10	23.8		7	14.9
PD	4	9.5		8	17.0
Missing	18	42.9		23	48.9
CR+PR(rate)[1]		23.8			19.2
(95% C.I.)					
Within Grp.[2]		(12.1, 39.5)			(9.2, 33.3)
Between Grp.[3]			4.7 (-12.6, 21.9)		

1. Denominator for response rate=number of randomized patients
2. 95% confidence interval for treatment group response rate.
3. 95% confidence interval for difference between response rates of the treatment groups (PDT - Nd:YAG). The O'Brien-Fleming method was used to adjust the width of the confidence interval [35].

References: Appendices IV, IX.E

PHOTOF 9401700IT1
03/15/94 (M11/AL5-59)

Table 12V.1. Distribution of Objective Response at Week 1 and Month 1 During the Second Course by Treatment Group

VISIT/ GRADE	Evaluable Assessments PDT NO.	PTS. %		Nd:YAG NO.	PTS. %
Randomized					
Week 1	28	100		23	100
CR1	1	3.57		0	0.0
CR2	0	0.0		0	0.0
CR3	0	0.0		0	0.0
PR	17	60.7		14	60.9
SD	10	35.7		9	39.1
PD	0	0.0		0	0.0
Missing	14			24	
CR+PR (rate)[1]		64.3			60.9
(95% C.I.) Within Grp.[2]		(44.1, 81.4)			(38.5, 80.3)
Between Grp.[3]			3.4(-23.5, 30.4)		
Month 1	23	100		24	100
CR1	2	8.70		0	0.0
CR2	0	0.0		0	0.0
CR3	0	0.0		0	0.0
PR	8	34.8		9	37.5
SD	10	43.5		7	29.2
PD	3	13.0		8	33.3
Missing	19			23	
CR+PR(rate)[1]		43.5			37.5
(95% C.I.) Within Grp.[2]		(23.19, 65.51)			(18.8, 59.5)
Between Grp.[3]			6.0 (-22.3, 34.3)		

1. Denominator for response rate=number of patients with evaluable assessments.
2. 95% (confidence interval) for treatment group response rate.
3. 95% (confidence interval) for difference between response rates of the treatment groups (PDT - Nd:YAG). The O'Brien-Fleming method was used to adjust the width of the confidence interval [35].

References: Appendices IV, IX.E

Table 12W. Change From Baseline in KPS at Second Course by Treatment Group

	All Available Grades			
	PDT		Nd:YAG	
VISIT	NO. PTS.	AVG. SCORE	NO. PTS.	AVG. SCORE
Baseline	42	78.93	47	77.87
Week 1	35	75.71	29	75.86
Change	35	-4.00	29	-1.72
(95% C.I.)				
Within Grp.[1]		(29.85, 61.33)		(-5.50, 2.05)
Between Grp.[2]		-2.28(-7.55, 3.00)		
Month 1	27	76.30	26	73.08
Change	27	-5.19	26	-6.15
(95% C.I.)				
Within Grp.[1]		(-9.29, -1.08)		(-10.65, -1.65)
Between Grp.[2]		0.97(-5.17, 7.11)		
Month 2	7	87.14	7	72.86
Change	7	-1.43	7	-5.71
*				
Month 3	2	80.00	0	
Change	2	-10.00	0	
*				
Month 6	1	90.00	0	
Change	1	0.00	0	
*				

1. 95% C.I. for within group mean change from baseline.
2. 95% C.I. for between group difference in mean changes from baseline. The O'Brien-Fleming method was used to adjust the width of the confidence interval [35].

* Confidence interval not calculated, too few patients to assess.

References: Appendices IV, IX.F

91A

PHOTOF 94017001T1
03/15/94 (M11/AL5-61)

TABLE 38. Course 2 Luminal Diameters (cm) and Changes From Baseline

All Available Data

Visit	P19			P20
	PDT	Nd:YAG	Difference (PDT-Nd:YAG)	PDT
BASELINE				
Mean luminal diameter (n)[a]	0.76 (34)	0.68 (45)		0.61 (8)
WEEK 1				
Mean luminal diameter (n)[a]	1.09 (29)	1.05 (23)		0.86 (7)
Mean change (n)[b]	0.33 (26)	0.41 (23)	(-0.09)	0.30 (7)
[95% CI[c]-mean change]	[0.19, 0.46]	[0.25, 0.57]	[-0.30, 0.13]	[-0.19, 0.79]
MONTH 1				
Mean luminal diameter (n)[a]	0.99 (23)	0.72 (25)		0.47 (3)
Mean change (n)[b]	0.16 (22)	0.08 (24)	(0.08)	-0.06 (3)[d]
[95% CI-mean change]	[0.01, 0.30]	[-0.06, 0.22]	[-0.12, 0.28]	
MONTH 2				
Mean luminal diameter (n)[a]	0.72 (5)	0.65 (4)		0.45 (2)
Mean change (n)[b]	-0.04 (5)[d]	-0.08 (4)[d]	(0.03)[d]	-0.04 (2)[d]
[95% CI-mean change]				

[a] (n) represents the number of patients with assessments at this visit.

[b] Negative changes indicate improvements from baseline, positive changes indicate worsening. (n) represents the number of patients with assessments both at this visit and at baseline.

[c] CI = Confidence Interval, adjusted using O'Brien-Fleming Procedure for the between-group comparison to reflect the interim analysis

[d] Too few patients

TABLE 39. Course 2 Luminal Diameters (cm) and Changes From Baseline

All Evaluable Data

Visit	P19			P20
	PDT	Nd:YAG	Difference (PDT-Nd:YAG)	PDT
BASELINE				
Mean luminal diameter (n)[a]	0.76 (34)	0.68 (45)		0.61 (8)
WEEK 1				
Mean luminal diameter (n)[a]	1.10 (28)	1.05 (23)		0.87 (6)
Mean change (n)[b]	0.34 (25)	0.41 (23)	-0.07	0.33 (6)
[95% CI[c]-mean change]	[0.21, 0.48]	[0.25, 0.57]	[-0.28, 0.15]	[-0.24, 0.91]
MONTH 1				
Mean luminal diameter (n)[a]	0.89 (22)	0.72 (24)		0.47 (3)
Mean change (n)[b]	0.16 (21)	0.08 (24)	(0.08)	-0.06 (3)
[95% CI-mean change]	[0.02, 0.31]	[-0.06, 0.22]	[-0.12, 0.29]	[d]
MONTH 2				
Mean luminal diameter (n)[a]	0.72 (5)	0.65 (4)		0.45 (2)
Mean change (n)[b]	-0.04 (5)	-0.08 (4)	(0.03)	-0.04 (2)
[95% CI-mean change]	[d]	[d]	[d]	[d]

[a] (n) represents the number of patients with evaluable assessments at this visit.
[b] Negative changes indicate improvements from baseline, positive changes indicate worsening. (n) represents the number of patients with evaluable assessments both at this visit and at baseline.
[c] CI = Confidence Interval, adjusted using O'Brien-Fleming Procedure for the between-group comparison to reflect the interim analysis
[d] Too few patients

Table 12Y. Summary of Survival for All Patients by Treatment Group

	PDT NO. PTS.	PDT (%)	Nd:YAG NO. PTS.	Nd:YAG (%)
Randomized	118	100.0	118	100.0
Number Dead	103	87.3	101	85.6
Number Censored	15	12.7	17	14.4
Alive	4		8	
Lost to follow-up	11		9	
Median TTF (days) [95% C.I.][a]	123 [94,148]		140 [112,176]	
Range				
Wilcoxon Chi-square (1 df)/p-value	0.190/0.6626			
Mantel-Cox Chi-square (1 df)/p-value	0.042/0.8371			
Hazard Ratio (Nd:YAG/PDT)[c]	0.97			
[95% CI]	[0.74,1.28]			

[a] Brookmyer - Crowley Method.
[b] Censored observation.
[c] Adjusted for using O'Brian-Fleming procedure.

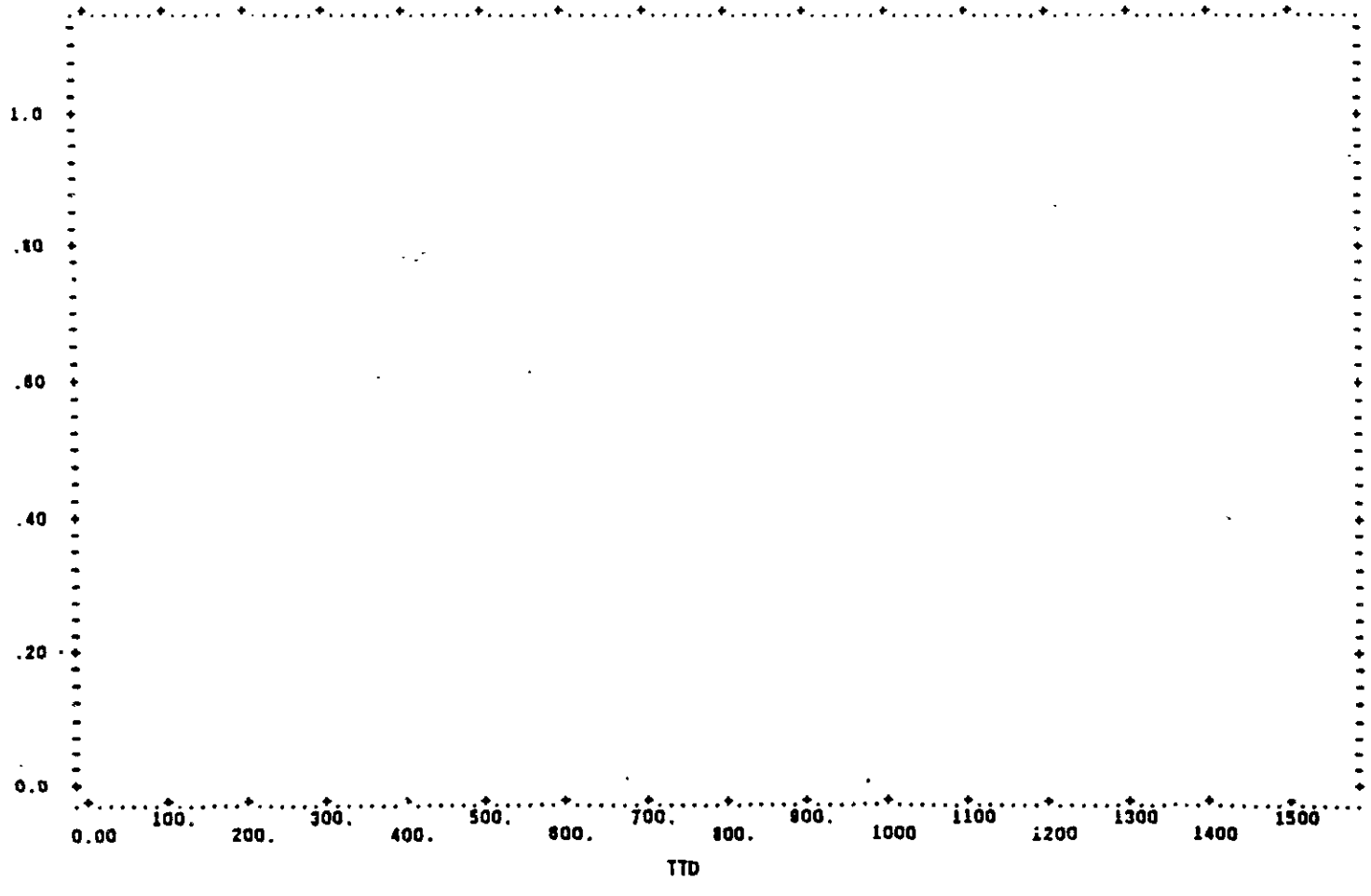
References: Appendices IV, X.F

92A

PHOTOF 94017001T1
03/15/94 (M11/AL5-63)

D73P19

Figure 4. Analysis Of Survival For All Patients



F is PDT Y is YAG

TABLE 56. Course 1 Subset Presentation of Dysphagia Analysis by PHOTOFRIN Formulation

All Available Data

Visit	P19 Frozen	P19 Lyophilized	Difference[a]
BASELINE			
n	43	67	
Mean dysphagia grade	3.07	2.78	
WEEK 1			
n	33	60	
Mean dysphagia grade	2.03	2.32	
Mean change	-1.15	-0.5	-0.65
[95% CI on mean change]	[-1.62, -0.68]	[-0.77, -0.23]	[-1.20, -0.11]
MONTH 1			
n	29	46	
Mean dysphagia grade	2.07	2.11	
Mean change	-0.93	-0.63	-0.3
[95% CI on mean change]	[-1.45, -0.41]	[-0.92, -0.34]	[-0.91, 0.31]

[a] Difference in response rates (frozen-lyophilized)

TABLE 57. Course 1 Subset Presentation of Objective Tumor Response by PHOTOFRIN Formulation

All Available Data

Number (%) of Patients

Visit	P19 Frozen		P19 Lyophilized		Difference[a]
WEEK 1					
n	43		67		
CR + PR	23	(53)	30	(45)	(9)
[95% CI][a]					[-11, 28]
SD + PD	9	(21)	23	(34)	
Missing	11	(26)	14	(21)	
MONTH 1					
n	43		67		
CR + PR	15	(35)	23	(34)	(1)
[95% CI][b]					[-18, 19]
SD + PD	13	(31)	18	(27)	
Missing	15	(35)	26	(39)	

[a] 95% confidence interval on rate of response
[b] Difference (frozen-lyophilized)

Table 13I. Number (Percentage) of Treated Patients Reporting at Least One Treatment-Related Adverse Event, by Body System, Individual Adverse Experience Within Body System and Treatment Group: Treatment-Related Events for Which the Treatment Difference in Incidence is at Least 5%, Based on All Treated Patients

	PDT No. (%)	Nd:YAG No. (%)	Treatment Comparison p-value*
No. of Treated Pts.	110 (100)	108 (100)	
At Least One AE (any severity)	73 (66.4)	40 (37.0)	p <0.01
At Least One AE (severe or life-threatening)	21 (19.1)	19 (17.6)	
Type of Event			
All Skin and Appendages	22 (20.0)	0 (0.0)	p <0.01
Photosensitivity Reaction	21 (19.1)	0 (0.0)	p <0.01
All Gastrointestinal	37 (33.6)	25 (23.1)	p =0.13
Nausea	9 (8.2)	2 (1.9)	p =0.03
All Respiratory	26 (23.6)	14 (13.0)	p =0.06
Pleural Effusion	11 (10.0)	2 (1.9)	p =0.01
All Body as a Whole	36 (32.7)	18 (16.7)	p =0.01
Fever	17 (15.5)	5 (4.6)	p <0.01

* Treatment groups were compared with respect to the distribution of ordered severity scores (none, mild, moderate, severe, very severe/life-threatening) using a (two-sided) Wilcoxon test.

References: Appendices IV, X.D

Zimmerman

Statistical Review and Evaluation

(NDA Supplement Review)

Date: June 7, 1995

NDA No.:	NDA 20451
Applicant:	QLT
Drug Name:	Photofrin® (Sterile Porfimer Sodium)
Documents Reviewed:	Response No. 44
Volume No:	Page 79-80 of Vol 1 and Appendix 16 of Vol 3
Data Source:	Document

Table of Contents

1. Summary

The stability analysis detailed in Appendix 16 (Vol. 3) was reviewed for evidence of compliance with the FDA guideline. The reviewer's analysis was consistent with the sponsor's. Namely, the expiration date was set to 18 months at temperature 30^0 C or lower.

2. The Sponsor's Analysis

Three batches of Photofrin® (Sterile Porfimer Sodium), packaged in 75 mg/vials, were stored at 30^0 C. The batches were identified as batch #910001, #910004, and #920005, respectively. The assays were conducted at 0, 1, 3, 6, 9, 12, 15, and 18 months; and finally, 21 or 24 months. Two major steps were taken to establish the expiration date:

(1) Test the betch-to-batch differences;
(2) Decide the expiration date.

The sponsor concluded that the degradation rates among batches had different intercepts and a common slop. This statistical model had a 25% change of misspecification solely due to random error. The estimated common slop, which represented the common degradation rate (per month), was -0.1749 % label claim per month. The expiration date was at least 18 months when the drug was kept at no more than 30^0 C.

3. The Reviewer's Analysis

The reviewer used the data provided on page 189 of the Appendix. Missing observations existed in each batch. A printout of observed percent label claims at different time points was shown on page A-1.

The poolability test, or the test of batch-to-batch differnece showed that the batches had a common degradation rate due to a p-value 0.68 (page A-2). The estimated common slop, which represented the common degradation rate (per month), was -0.1749 % label claim per month. The initial label claims were estimated to be 101.05%, 98.77% and 102.33% for batch #910001, #910004, and #920005, respectively. These numbers were the same as the sponsor's. The estimated expiration dates for these batches were 37, 29 and 40 months (page A-3, and A-4 to A-6). Note that these dates represented the extrapolated from the observed label claims, and the last observation was made at 24 months. Based on the FDA Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics[1], unless the trends of degradation over time were validated by the future data submission, the expiration date could only be decided from the observed data. Therefore, the data support the requested expiration date of 18 months.

The reviewer concluded that the sponsor's analysis was properly conducted and the sponsor's conclusion was correct.

Ted Guo

Ted (Ji-Yang) Guo, Ph.D.
Mathematical Statistician

Karl K. Lin 6/7/95

Concur: Karl K. Lin, Ph.D., Group Leader, CDER

cc: NDA 20-451, Supplement Review
HFD-151/Paul F. Zimmerman
HFD-150/Yung Ao Hsieh
HFD-715/Karl K. Lin
HFD-715/Ted Guo
HFD-715/Chron
HFD-715/SARB Chron.
HFD-715/DRU 2.1.1, NDA 20-451, Photofrin® (Sterile Porfimer Sodium), Supplement Review

References

1. Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics. 1987. pp. 38.

Appendix

Stability Analysis
Sponsor: QLT
NDA 20-451 Photofrin
Package: 75 mg/vial
Sterile Porfimer Sodium
Temperature: 30 Degrees Centigrade

TIME	_910001	_910004	_920005
0	104.40	99.55	106.75
1	104.60	97.70	104.10
3	97.00	97.90	96.15
6	97.00	96.60	98.20
9	.	95.30	98.65
12	99.60	99.55	102.25
15	.	93.95	98.50
18	.	98.45	102.85
21	97.60	.	.
24	95.45	.	.

Stability Analysis
Sponsor: QLT
NDA 20-451 Photofrin
Package: 75 mg/vial
Sterile Porfimer Sodium
Temperature: 30 Degrees Centigrade

SOURCE	SS	DF	MS	F	P
A	59.11	4	14.78	1.59653	0.22078
B	51.79	2	25.90	2.79786	0.08904
C	7.32	2	3.66	0.39519	0.67958
D	157.35	17	9.26		
E	226528.24	6	37754.71		

****
* Statistical Analysis: *
* Key to sources of variation *
* A = sep. intercep, sep slope \| com intercep, com slope *
* B = sep. intercep, com slope \| com intercep, com slope *
* C = sep. intercep, sep slope \| sep intercep. com slope *
* D = Residual *
* E = Full Model *
****

Stability Analysis
Sponsor: QLT
NDA 20-451 Photofrin
Package: 75 mg/vial
Sterile Porfimer Sodium
Temperature: 30 Degrees Centigrade
95% One-Sided Lower Confidence Limit

Separate Intercepts and Common Slope

BATCH	ESTIMATED DATING PERIOD (MONTH)
#910001	37
#910004	29
#920005	40

/Courier

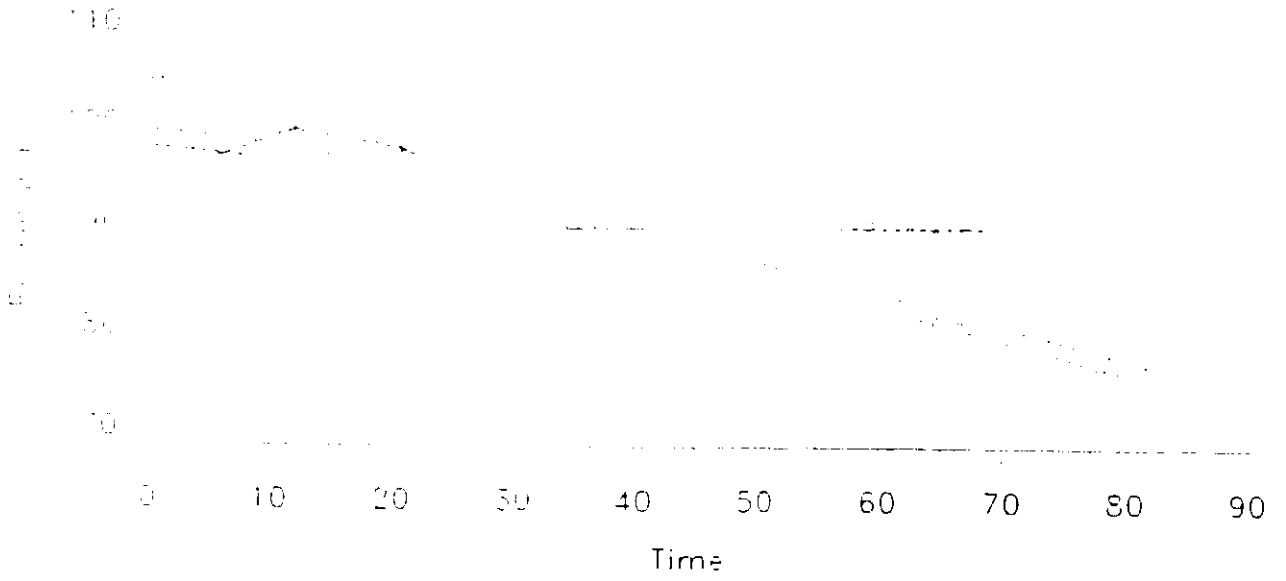
Stability Analysis

Sponsor: OLT

A-4

NDA 20-451 Photofrin
Package: 75 mg/vial
Sterile Porfimer Sodium
Temperature: 30 Degrees Centigrade

BATCH=-910001



Legend: Percent of Claim Predicted
Lower Bound

/Courier

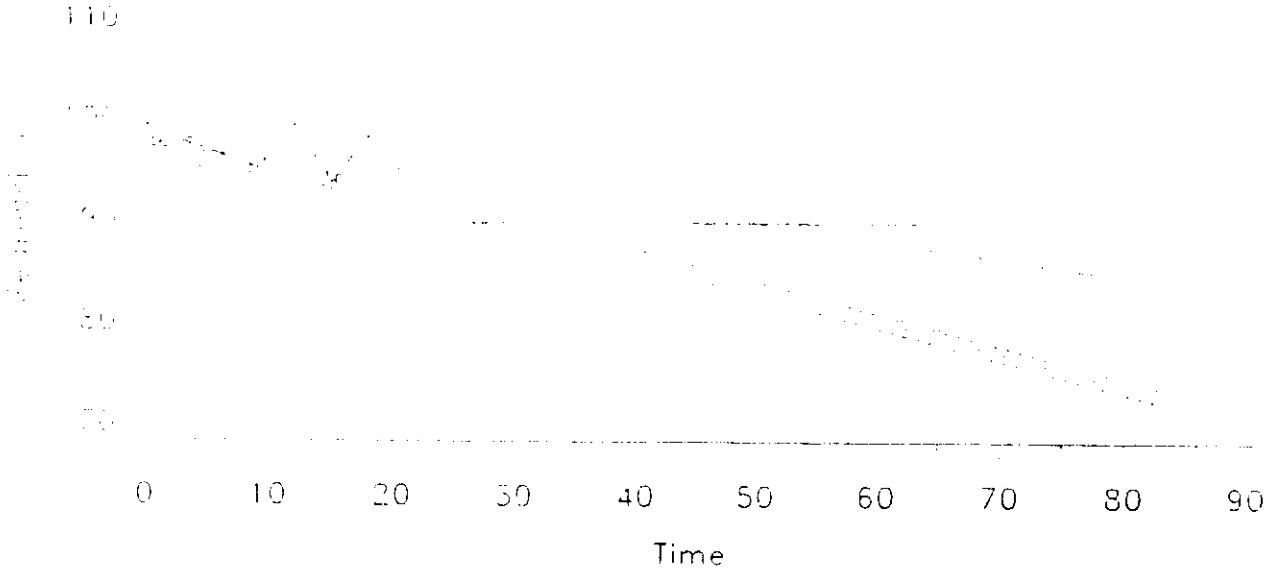
Stability Analysis

Sponsor: QLT

A-5

NDA 20--451 Photofrin
Package: 75 mg/vial
Sterile Porfimer Sodium
Temperature: 30 Degrees Centigrade

BATCH==910004



Legend: Percent of Claim Predicted
Lower Bound

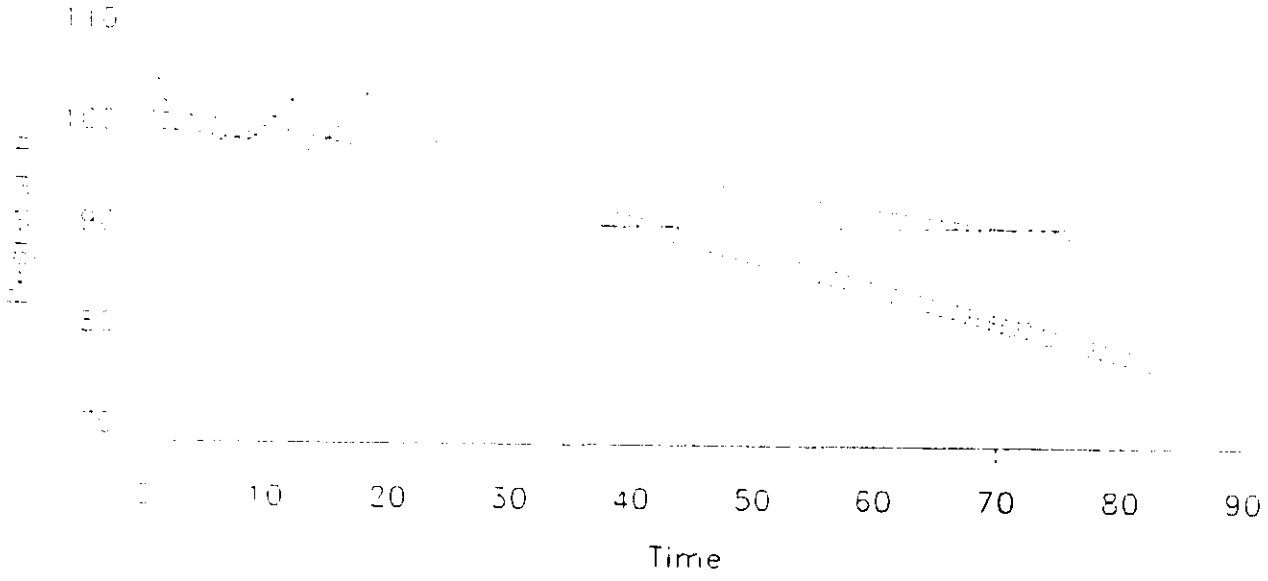
/Courier

Stability Analysis

Sponsor: QLT

NDA 20-451 Photofrin
Package: 75 mg/vial
Sterile Porfimer Sodium
Temperature: 30 Degrees Centigrade

BATCH=#920005



Legend: Percent of Claim
Lower Bound
Predicted

HFD-150
Yung Hsieh

Statistical Review and Evaluation

(NDA Supplement Review)

Date: June 26, 1995

NDA No.:	NDA 20451
Applicant:	QLT Phototherapeutics Inc.
Drug Name:	Photofrin® (Sterile Porfimer Sodium)
Documents Reviewed:	Original NDA
Volume No:	Page 284-347 of Vol. 6
Data Source:	Document

Table of Contents

1. Introduction

The purpose of this report was to examine the evidence of compliance with the FDA Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics[1], and to review the term and statistical rationale for **accumulated change in test parameters**[1], which represented the area percentages of some compounds of Photofrin® (sterile porfimer sodium).

2. The Sponsor's Analysis

The sponsor detailed the statistical method on page 309-47, vol. 6 of the NDA submission. The definition of **accumulated change** was given on page 311, vol. 6. It was expressed as follows:

$$\beta \times t \pm t_{0.95}\sqrt{(s.e.(\beta)\times t)^2+\sigma^2},$$

where β was the regression coefficient of time t in the linear regression model that fitted a compound; time t, was the proposed shelf life; and σ^2 was the mean square error[2] in the linear model. This quantity described the maximum change between the initial value at the beginning of the test and the value at the shelf life. The explanation of this concept will be further detailed in the following section.

The sponsor claimed that the purpose of the estimates of the accumulated changes was to bridge the gap between release and shelf life specifications for this drug. The variables analyzed in this report were:

- Hematoporphrin (denoted as HP),
- Hydroxyethylvinyldeuterophyrin (denoted as HVD),
- Protoporphyrin (denoted as PP), and
- Total of HP, HVD and PP (denoted as TRC).

The above variables were presented (scaled) as area percentages. The drug was packaged in the format of 75 mg/vial and stored at 30° C. The proposed shelf life was 18 months.

---

[1] The test parameters are referred to the compounds of interest.

[2] The mean square error is calculated by dividing the sum of squares of error in the

Three batches of the drug were studied and tested at 0, 1, 3, 6, 9, 12, 15, 18, 21 and 24 months. The batches were marked as #910001, #910004, and #920005, respectively. Not all batches were tested at all these time points. Two major steps were taken to obtain the values of the accumulated changes:

(1) Test the batch-to-batch differences (test of poolability);
(2) Estimate the accumulated changes (increase or decrease), of the area percentages for the variables between the initial values and the values at the proposed shelf life.

As the results of the first step, The sponsor concluded that for variables HP, HVD and TRC, the fitted linear regression lines had a common slope and different intercepts among the batches. However, among the batches for PP, the regression lines had a common intercept and a common slope.

The accumulated changes for HP, HVD, PP, and TRC were 0.50, 0.86, 2.91, and 2.99, respectively. These estimated accumulated changes were located in Table 2, page 311, vol. 6 of the NDA submission.

3. The Reviewer's Explanation of the term **Accumulated Change**

Using an intuitive explanation of the **accumulated change**, suppose that the value of area percent of a variable would decrease (degrade) in time. For a future batch, the accumulated change is defined as the maximum difference between the predicted value at time 0 (beginning of the stability test) and the predicted value at the proposed shelf life. Because of the random nature of the prediction, confidence bound(s) are employed to predict this maximum change that satisfies a predetermined confidence level, say, 95%. In this case, a lower confidence bound for a predicted individual value (instead of a lower confidence bound for a mean value) is used. The following Figure 1 depicts how the accumulated change is measured. The variable used is the potency of porfimer sodium. This is simply an example.

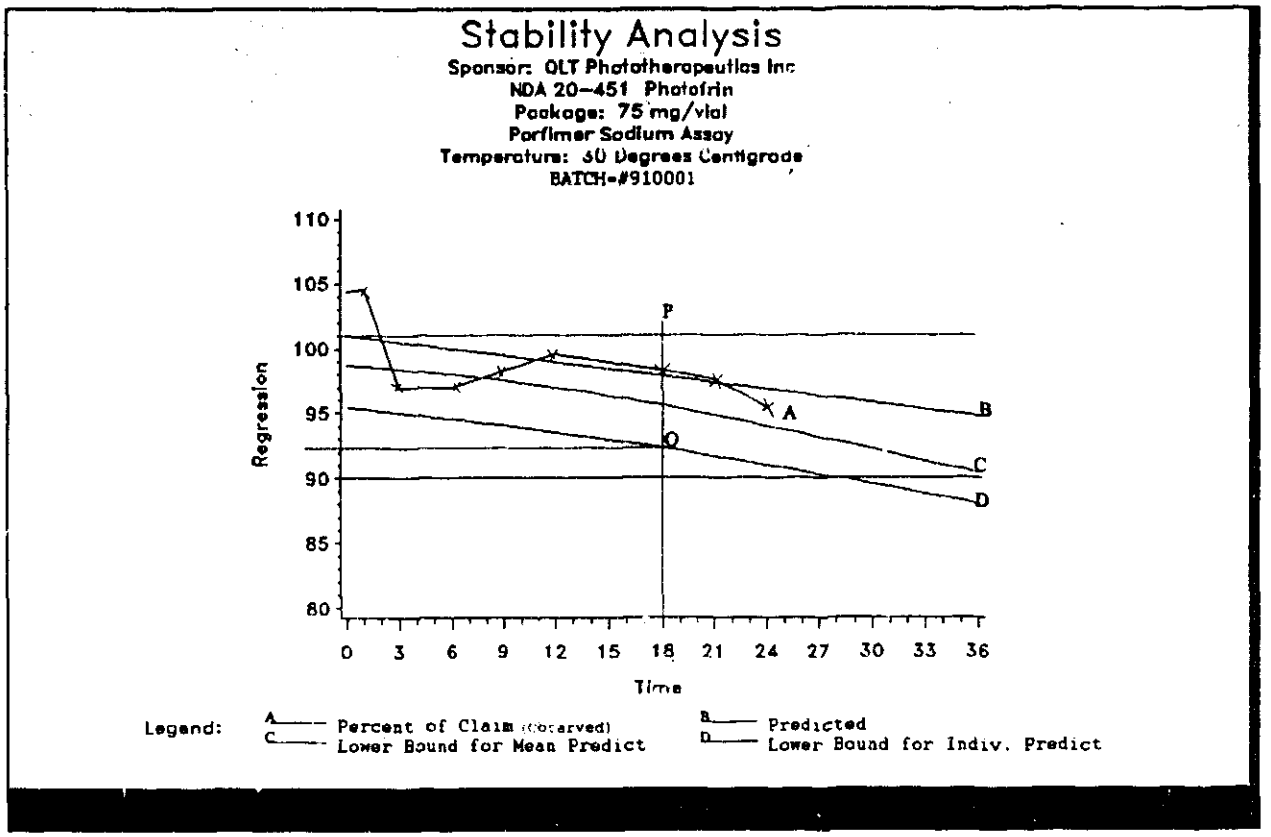


Figure 1. Illustration of **Accumulated Change**

As can be seen on Figure 1, curve D represents the lower confidence bound for the predicted individual value, while curve C is the lower confidence bound for the mean value. The curve D lies below C due to an extra term σ^2, one of the components that form the confidence bound. The length of PQ represents the accumulated change. It is approximately 8.9 measured directly from the graph, which is the same as the value calculated by the sponsor. Line A connects all observed data points.

It is important to note that when the linear regression lines for the batches do not have a common slope, the common accumulated change does not exist.

4. The Reviewer's Analysis

To verify the statistical results obtained by the sponsor, the reviewer performed the standard stability analyses on variables HP, HVD, PP, and TRC (as the total related compounds). The source data were input manually from page 317, 322, 327, and 332, vol. 6, NDA submission 20-451. The key printouts from the SAS runs were included in the appendix for reference. Also included in the appendix were graphs of the observed values, the regression lines, and the confidence bounds. The plots of the observed values were connected as line A.

The following table summarizes the analysis for the above 4 variables. The results of the test of batch-to-batch differences are noted in the column "Fitted Model." Using the same notation as the one used by the sponsor, "CSDI" denotes that the linear regression lines have a common slope but different intercepts among the batches, while "CSCI" denotes that the linear regression lines have both a common slope and a common intercept across the batches. The practical meaning of the slope is the amount of area percent increased or decreased per month. A positive sign in front of an accumulated change indicates an increase, otherwise, a decrease, if any. Note that the values in the parentheses are those obtained by the sponsor.

Variable (Area %)	Fitted Model	Batch No.	Predicted Intercept	Estimated Slope	Accumulated Change
HP	CSDI	910001	1.32	0.00267 (0.003)	+0.493 (+0.50)
		910004	1.72		
		920005	1.57		
HVD	CSDI	910001	6.96	-0.00298 (0.003)	+0.827 (+0.86)
		910004	7.58		
		920005	5.46		
PP	CSDI (CSCI)	910001	3.49	0.0894 (0.091)	+2.75 (+2.91)
		910004	3.60		
		920005	2.87		
TRC	CSDI	910001	11.7	0.0673 (0.067)	+2.98 (+2.99)
		910004	13.1		
		920005	10.1		

The discrepancies between the reviewer's results and the sponsor's can be seen in the above table. The reviewer found that the linear regression lines for PP had a common slope and different intercepts with a p-value 0.056, instead of a common slope and a common intercept concluded by the sponsor.

5. Conclusions

The reviewer concluded that the sponsor's definition of the **accumulated change** is valid, but some discrepancies in calculation exist. The linear regression lines had a common slope but different intercepts for HP, HVD, PP, and TRC.

Ted Guo

Ted (Ji-Yang) Guo, Ph.D.
Mathematical Statistician

Karl K. Lin 6/28/95

Concur: Karl K. Lin, Ph.D., Group Leader, CDER

cc: NDA 20-451, Supplement Review
HFD-150/Paul F. Zimmerman
HFD-150/Yung Ao Hsieh
HFD-715/Karl K. Lin
HFD-715/Ted Guo
HFD-715/Chron
HFD-715/SARB Chron.
HFD-715/DRU 2.1.1, NDA 20-451, Photofrin® (Sterile Porfimer Sodium), Supplement Review

5. References

1. Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics. 1987. pp. 38.

6. Appendix

Figures

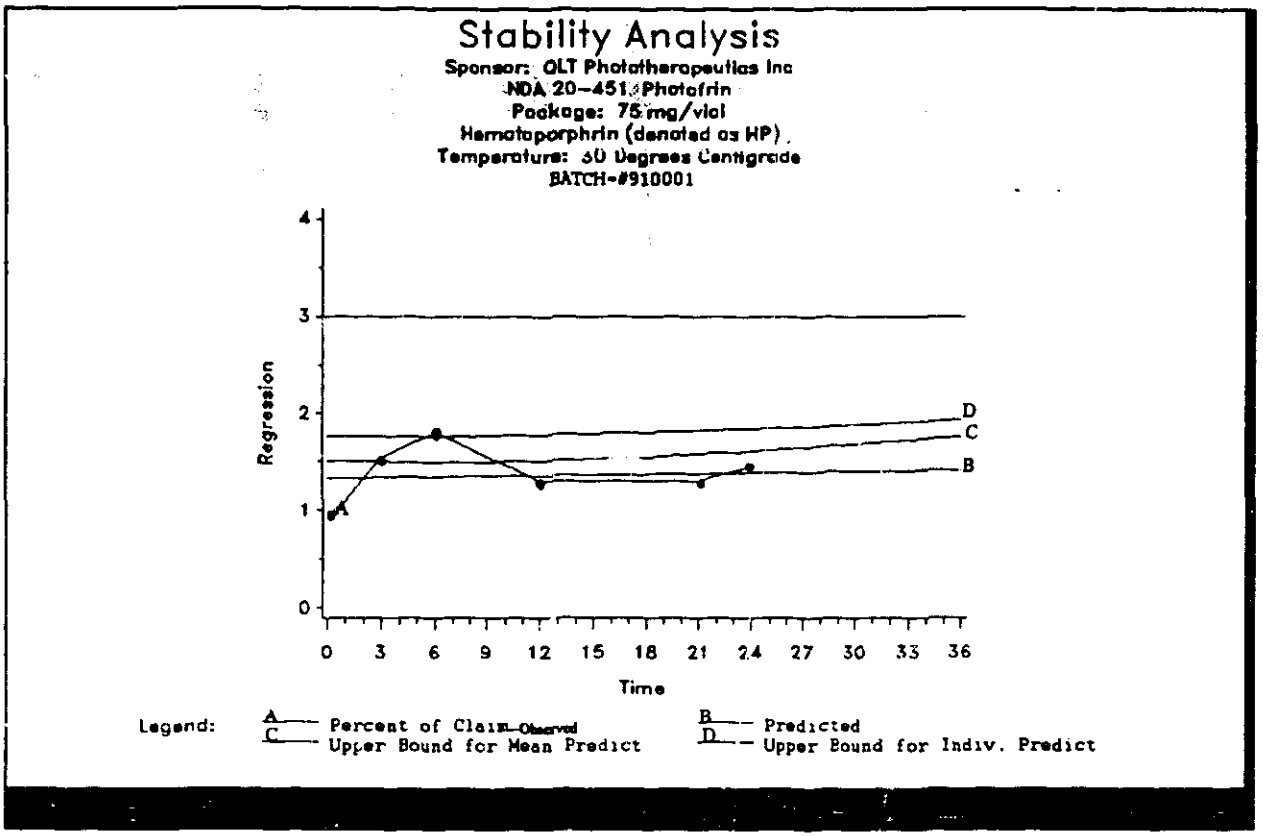


Figure 2. Hematoporphrin

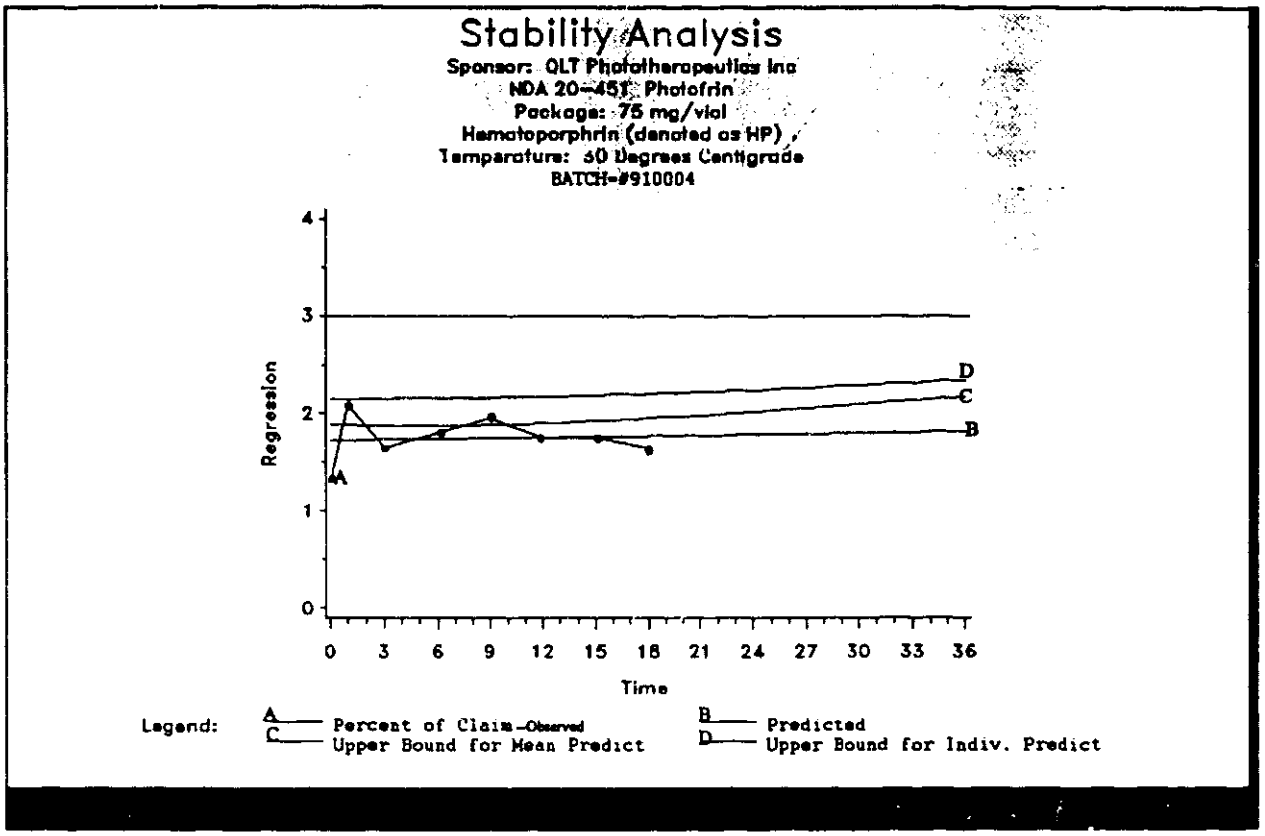


Figure 3. Hematoporphrin

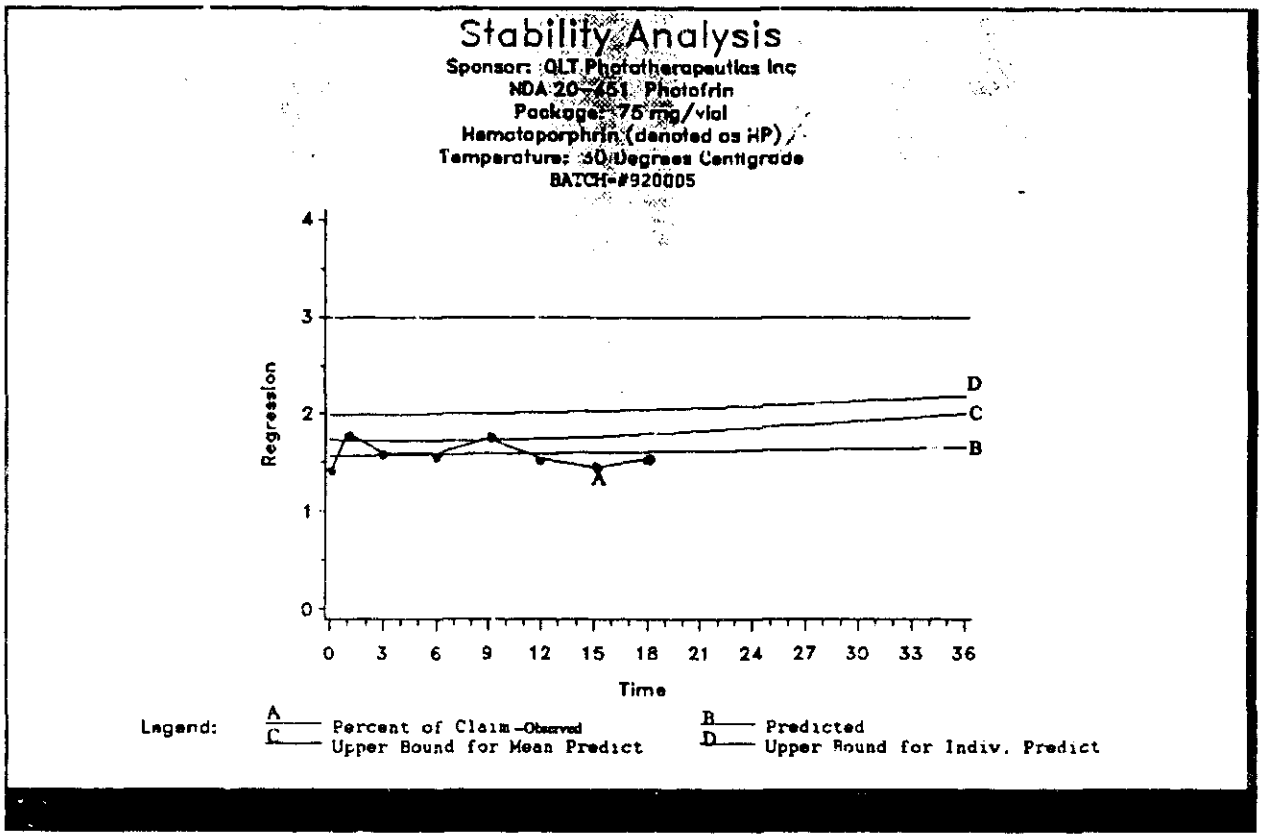


Figure 4. Hematoporphrin

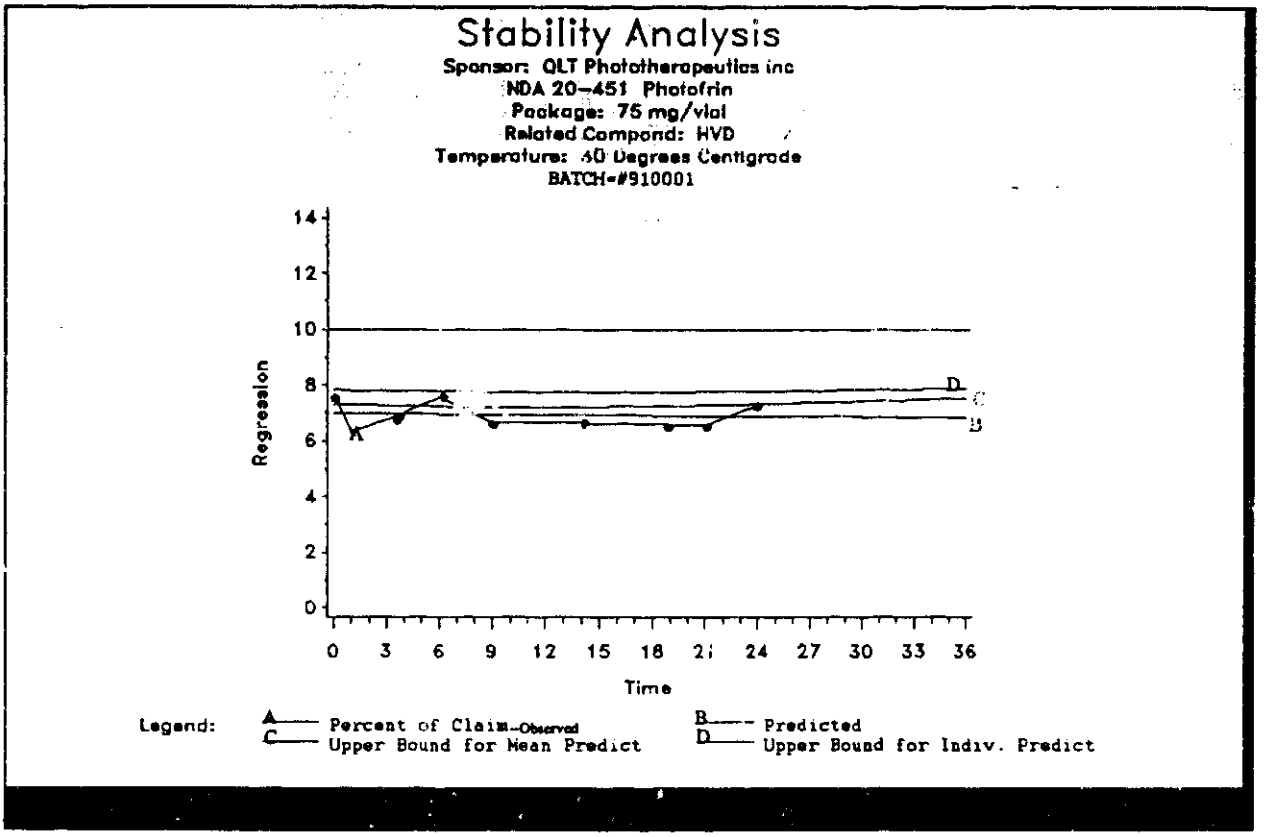


Figure 5. Hydroxyethylvinyldeuteroporphyrin

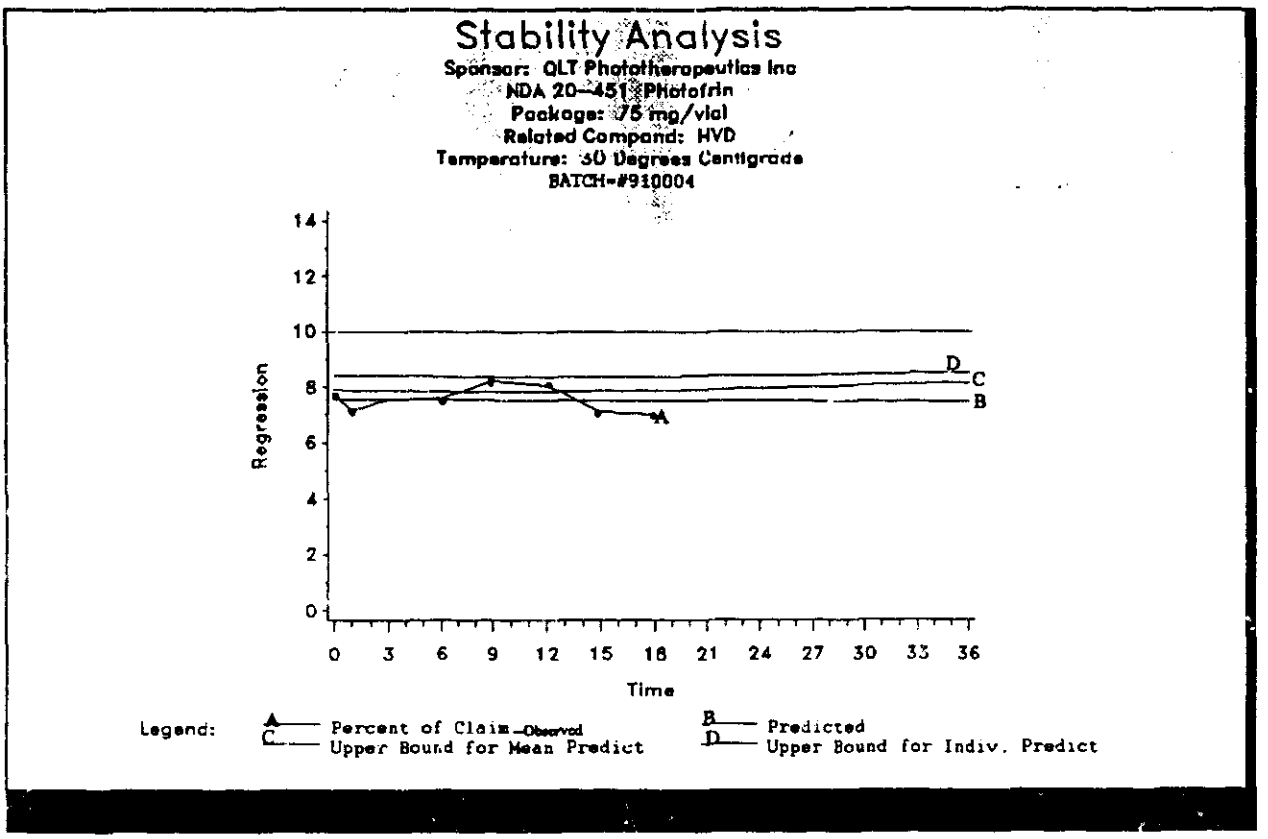


Figure 6. Hydroxyethylvinyldeuterophyrin

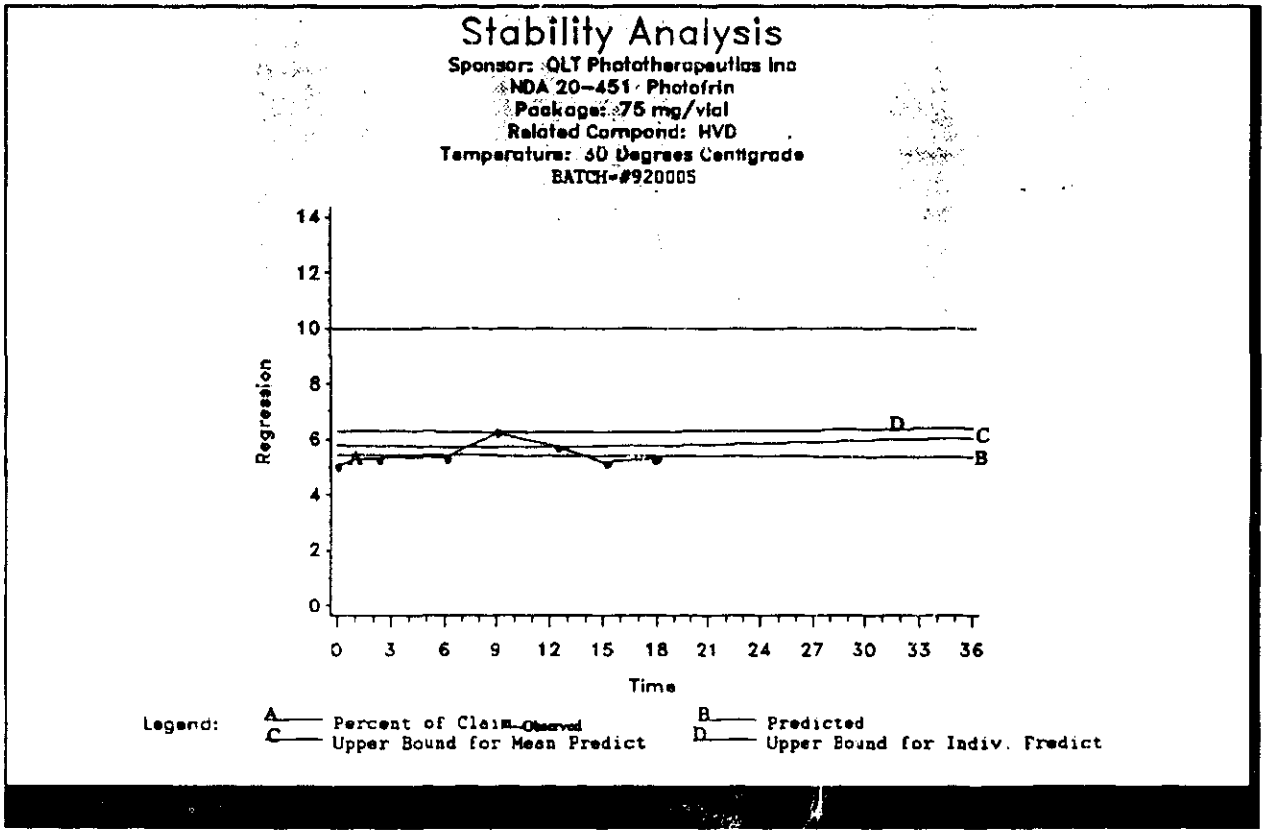


Figure 7. Hydroxyethylvinyldeuterophyrin

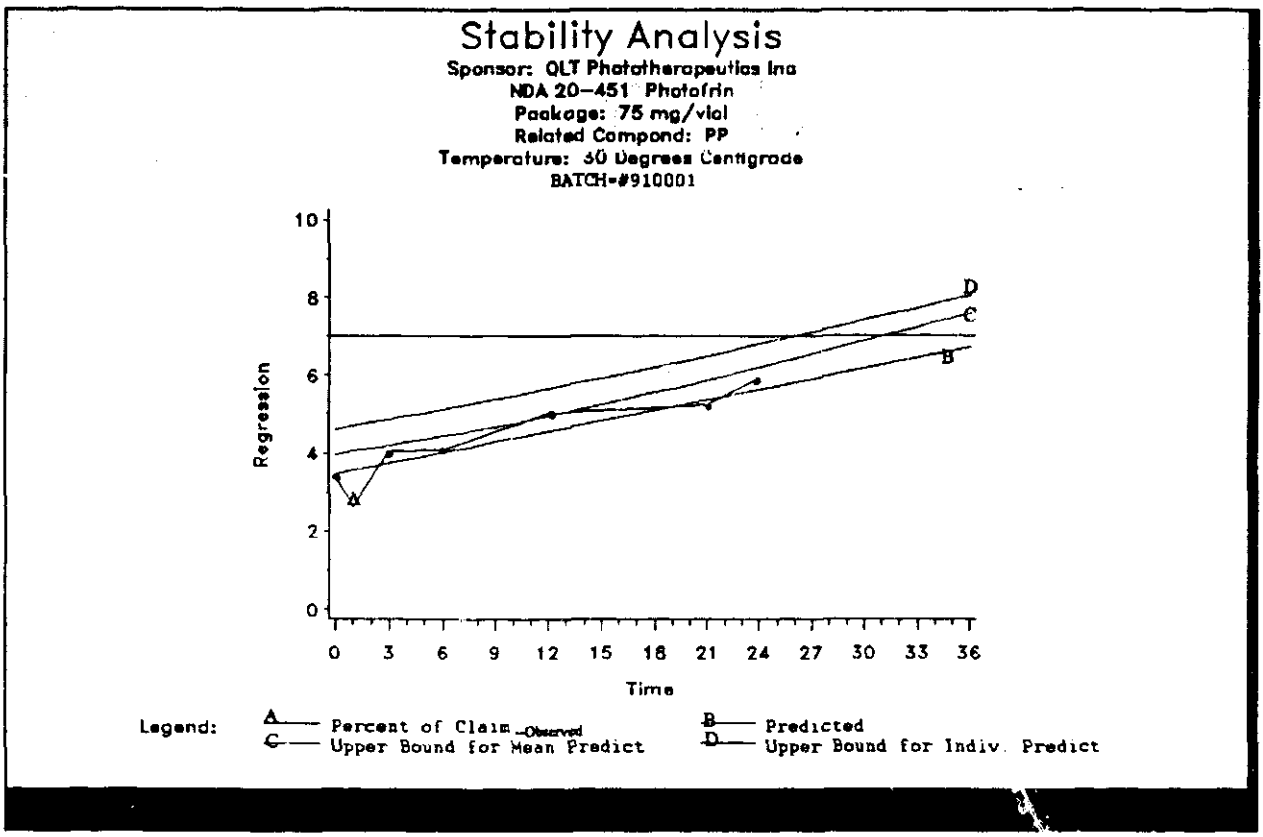


Figure 8. Protoporphyrin

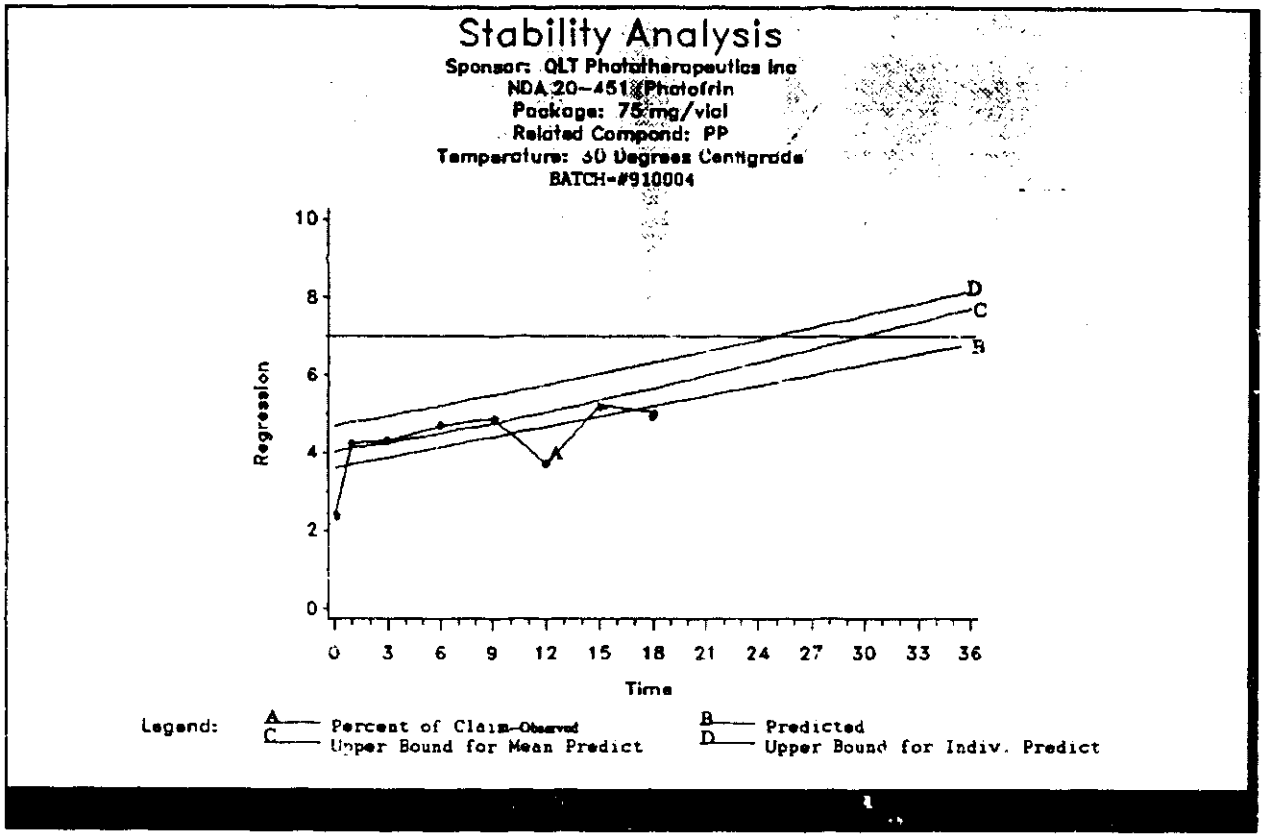


Figure 9. Protoporphyrin

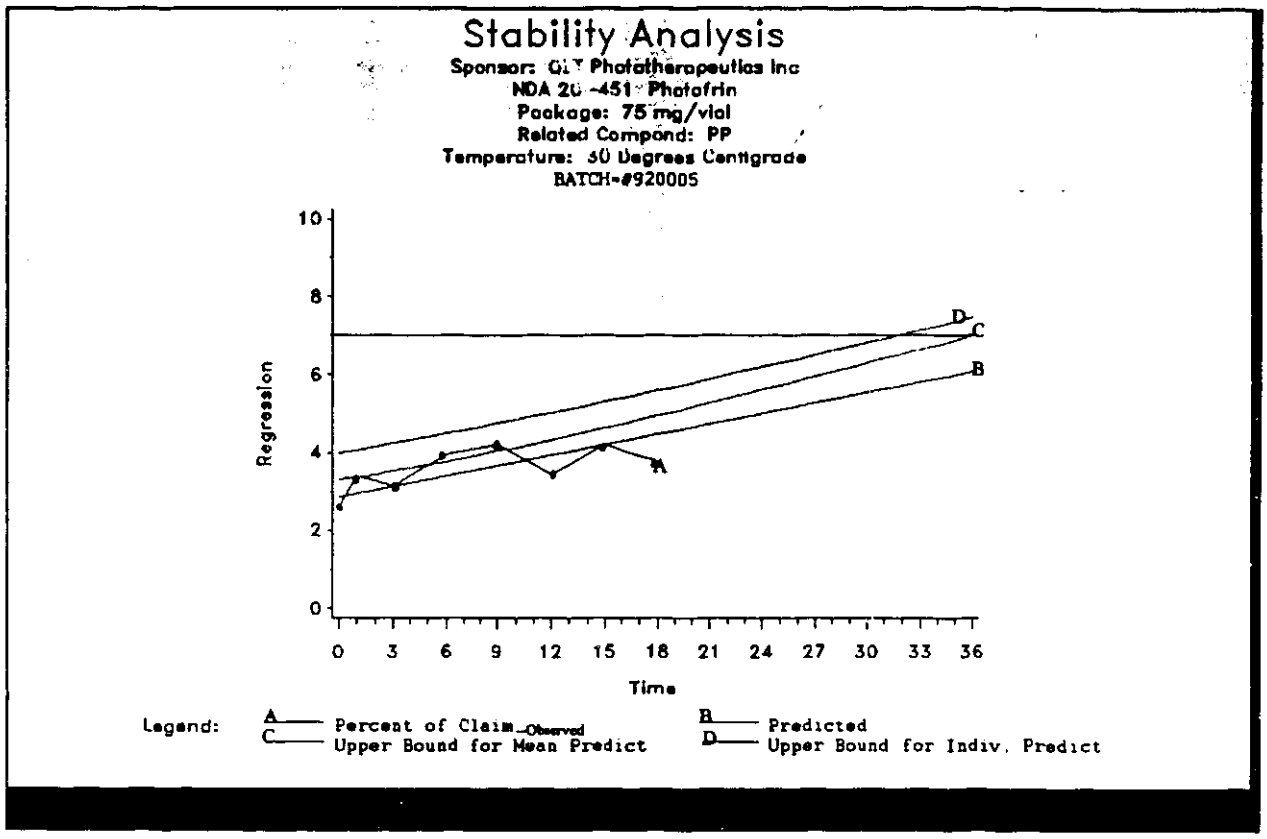


Figure 10. Protoporphyrin

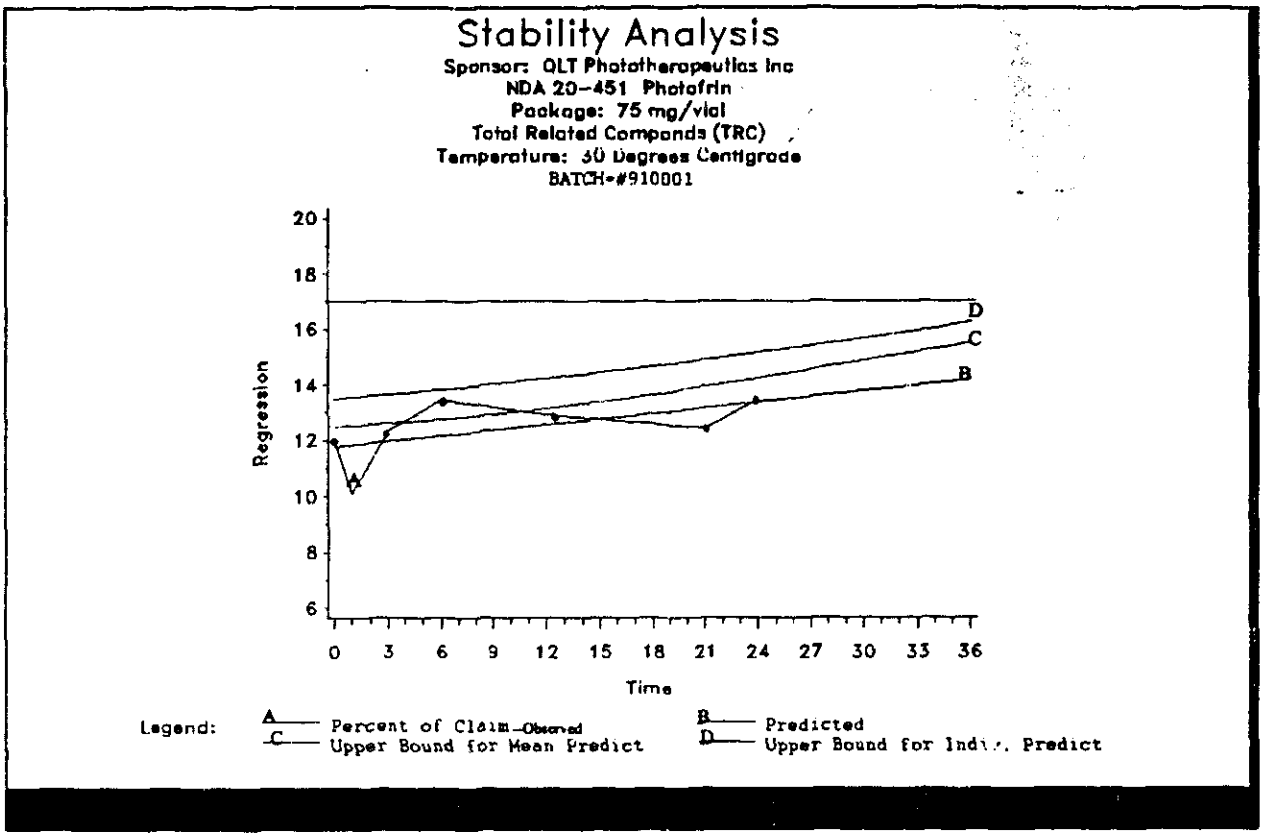


Figure 11. Total of HP, HVD and PP

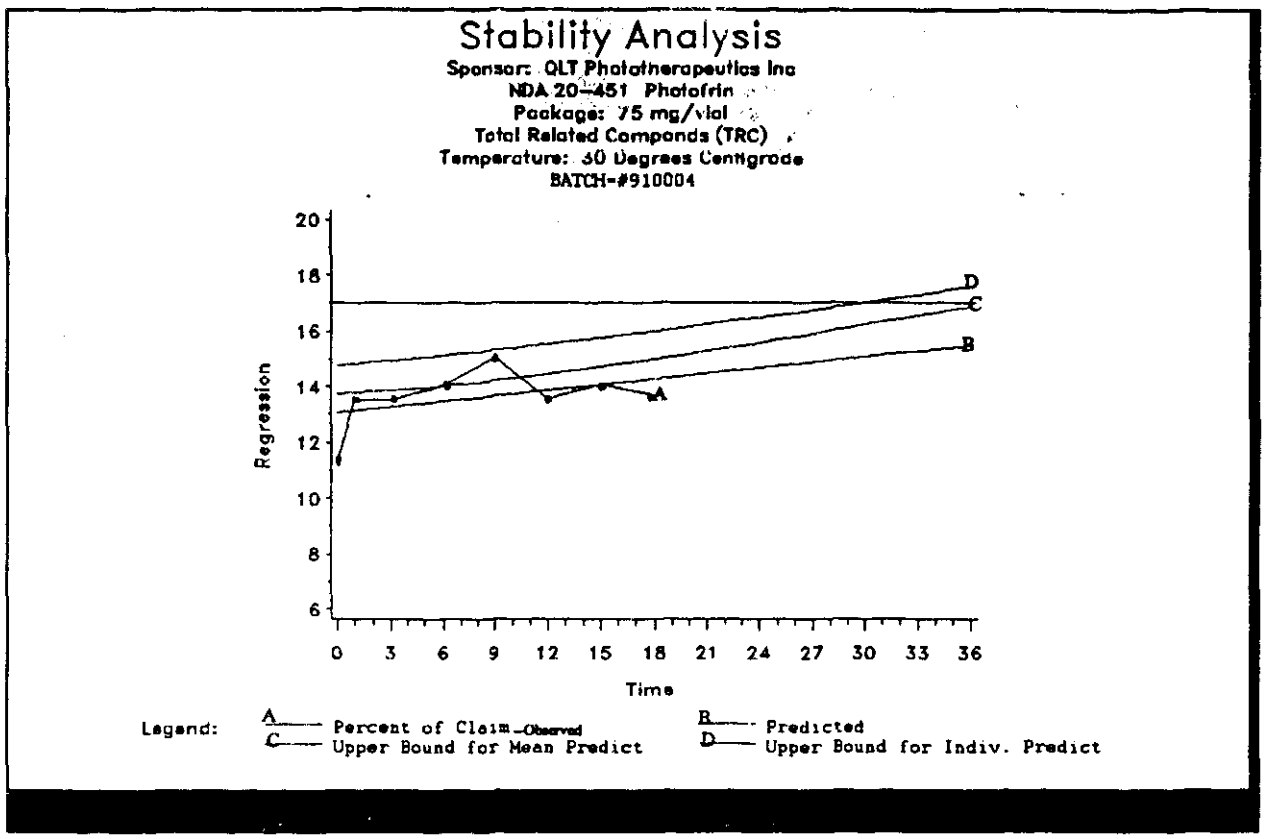


Figure 12. Total of HP, HVD and PP

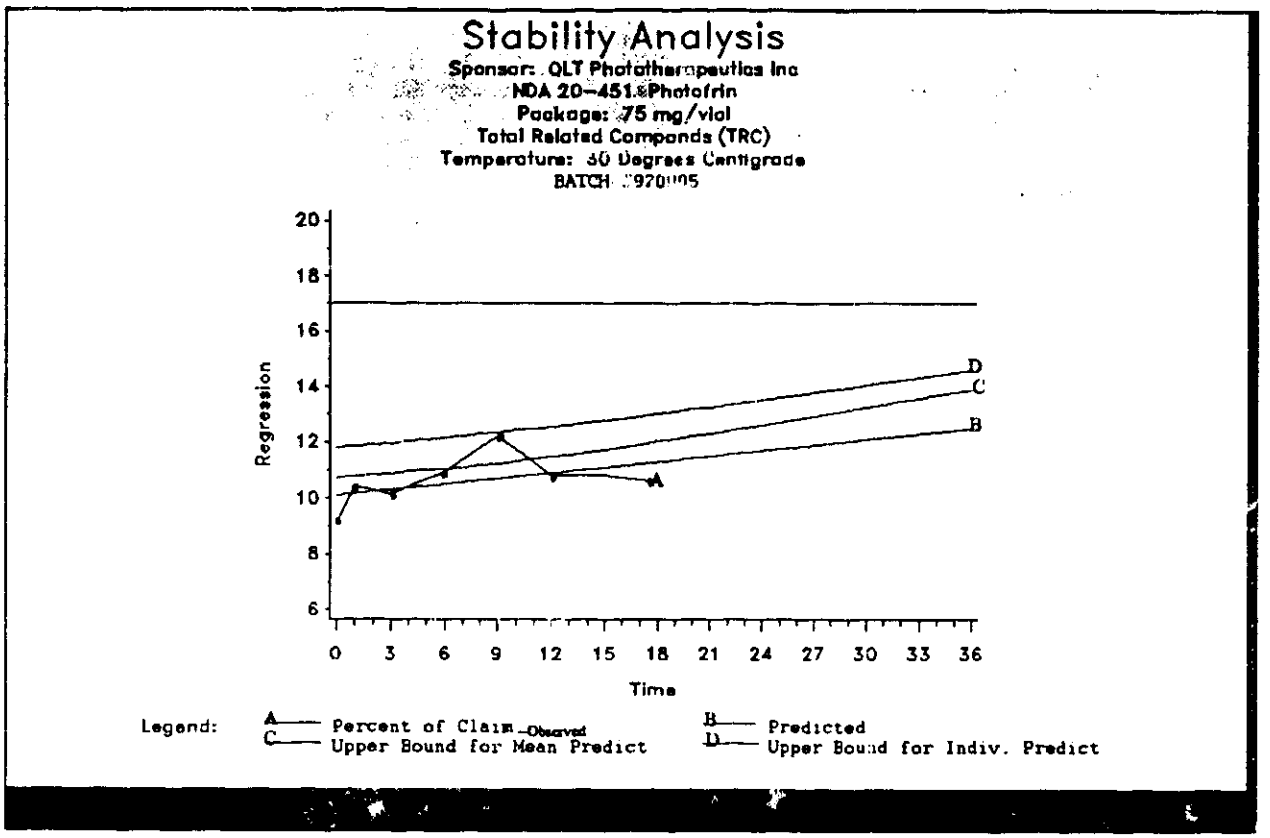


Figure 13. Total of HP, HVD and PP

Tables

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
HP (Hematoporphrin)
Temperature: 30 Degrees Centigrade

Time	_910001	_910004	_920005
0	0.95	1.30	1.40
1	1.10	2.10	1.80
3	1.55	1.65	1.60
6	1.80	1.80	1.60
9	.	1.95	1.75
12	1.30	1.75	1.55
15	.	1.75	1.45
18	.	1.65	1.55
21	1.30	.	.
24	1.45	.	.

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
HP (Hematoporphrin)
Temperature: 30 Degrees Centigrade

SOURCE	SS	DF	MS	F	P
A	0.6160	4	0.15401	2.72088	0.06436
B	0.5907	2	0.29535	5.21810	0.01710
C	0.0253	2	0.01266	0.22366	0.80191
D	0.9622	17	0.05660	.	.
E	57.2778	6	9.54630	.	.

```
**************************************************************
* Statistical Analysis:                                      *
*      Key to sources of variation                           *
* A = sep. intercep, sep slope | com intercep, com slope      *
* B = sep. intercep, com slope | com intercep, com slope      *
* C = sep. intercep, sep slope | sep intercep, com slope      *
* D = Residual                                               *
* E = Full Model                                             *
**************************************************************
```

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
HP (Hematoporphrin)
Temperature: 30 Degrees Centigrade
95% One-Sided Upper Confidence Limit

Separate Intercepts and Common Slope

BATCH	ESTIMATED DATING PERIOD (MONTH)
#910001	84
#910004	84
#920005	84

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
HP (Hematoporphrin)
Temperature: 30 Degrees Centigrade

Accumulated Changes at Proposed Shelf-Life From Initial Values

Slop Estimation	Slop Std. Err.	Mean Square Error	Degrees of Freedom	One Tailed Probalility	Critical Point	Accumulated Change
.002666	.006632	0.05198	19	0.0500	1.729	0.49295

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
HVD (Hydroxyethylvinyldeuterophyrin)
Temperature: 30 Degrees Centigrade

Time	_910001	_910004	_920005
0	7.65	7.75	5.10
1	6.35	7.15	5.25
3	6.75	7.55	5.35
6	7.55	7.60	5.35
9	6.65	8.25	6.20
12	6.65	8.05	5.80
15	.	7.10	5.20
18	.	7.00	5.30
21	6.55	.	.
24	7.30	.	.

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
HVD (Hydroxyethylvinyldeuterophyrin)
Temperature: 30 Degrees Centigrade

SOURCE	SS	DF	MS	F	P
A	18.98	4	4.744	21.4830	0.00000
B	18.85	2	9.427	42.6862	0.00000
C	0.12	2	0.062	0.2798	0.75918
D	3.97	18	0.221	.	.
E	1078.32	6	179.720	.	.

****
* Statistical Analysis: *
* Key to sources of variation *
* A = sep. intercep, sep slope \| com intercep, com slope *
* B = sep. intercep, com slope \| com intercep, com slope *
* C = sep. intercep, sep slope \| sep intercep, com slope *
* D = Residual *
* E = Full Model *
****

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
HVD (Hydroxyethylvinyldeuterophyrin)
Temperature: 30 Degrees Centigrade
95% One-Sided Upper Confidence Limit

Separate Intercepts and Common Slope

BATCH	ESTIMATED DATING PERIOD (MONTH)
#910001	84
#910004	84
#920005	84

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
HVD (Hydroxyethylvinyldeuterophyrin)
Temperature: 30 Degrees Centigrade

Accumulated Changes at Proposed Shelf-Life From Initial Values

Slop Estimation	Slop Std. Err.	Mean Square Error	Degrees of Freedom	One Tailed Probalility	Critical Point	Accumulated Change
-.00298	0.013167	0.20493	20	0.0501	1.724	0.82729

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
PP (Protoporphyrin)
Temperature: 30 Degrees Centigrade

Time	_910001	_910004	_920005
0	3.40	2.35	2.60
1	2.65	4.25	3.40
3	4.05	4.30	3.15
6	4.10	4.70	3.95
9	.	4.90	4.20
12	5.00	3.70	3.45
15	.	5.25	4.20
18	.	5.05	3.75
21	5.25	.	.
24	5.95	.	.

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
PP (Protoporphyrin)
Temperature: 30 Degrees Centigrade

SOURCE	SS	DF	MS	F	P
A	3.004	4	0.7511	2.13595	0.12066
B	2.410	2	1.2048	3.42609	0.05621
C	0.595	2	0.2974	0.84582	0.44649
D	5.978	17	0.3517	.	.
E	393.802	6	65.6337	.	.

```
**********************************************************
* Statistical Analysis:                                  *
*      Key to sources of variation                       *
* A = sep. intercep, sep slope | com intercep, com slope  *
* B = sep. intercep, com slope | com intercep, com slope  *
* C = sep. intercep, sep slope | sep intercep, com slope  *
* D = Residual                                           *
* E = Full Model                                         *
**********************************************************
```

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
PP (Protoporphyrin)
Temperature: 30 Degrees Centigrade
95% One-Sided Upper Confidence Limit

Separate Intercepts and Common Slope

BATCH	ESTIMATED DATING PERIOD (MONTH)
#910001	31
#910004	29
#920005	36

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
PP (Protoporphyrin)
Temperature: 30 Degrees Centigrade

Accumulated Changes at Proposed Shelf-Life From Initial Values

Slop Estimation	Slop Std. Err.	Mean Square Error	Degrees of Freedom	One Tailed Probalility	Critical Point	Accumulated Change
0.089386	0.017109	0.34594	19	0.0500	1.729	2.75685

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
TRC (Total Related Compounds)
Temperature: 30 Degrees Centigrade

Time	_910001	_910004	_920005
0	12.00	11.35	9.10
1	10.10	13.50	10.40
3	12.35	13.50	10.15
6	13.45	14.05	10.95
9	.	15.10	12.20
12	12.95	13.55	10.80
15	.	14.10	10.80
18	.	13.70	10.55
21	12.45	.	.
24	13.45	.	.

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
TRC (Total Related Compounds)
Temperature: 30 Degrees Centigrade

SOURCE	SS	DF	MS	F	P
A	35.91	4	8.976	9.7798	0.00027
B	35.85	2	17.924	19.5279	0.00004
C	0.06	2	0.029	0.0317	0.96882
D	15.60	17	0.918	.	.
E	3463.59	6	577.266	.	.

****
* Statistical Analysis: *
* Key to sources of variation *
* A = sep. intercep, sep slope | com intercep, com slope *
* B = sep. intercep, com slope | com intercep, com slope *
* C = sep. intercep, sep slope | sep intercep, com slope *
* D = Residual *
* E = Full Model *
****

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
TRC (Total Related Compounds)
Temperature: 30 Degrees Centigrade
95% One-Sided Upper Confidence Limit

Separate Intercepts and Common Slope

BATCH	ESTIMATED DATING PERIOD (MONTH)
#910001	49
#910004	37
#920005	63

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
TRC (Total Related Compounds)
Temperature: 30 Degrees Centigrade

Accumulated Changes at Proposed Shelf-Life From Initial Values

Slop Estimation	Slop Std. Err.	Mean Square Error	Degrees of Freedom	One Tailed Probalility	Critical Point	Accumulated Change
0.067299	0.026411	0.82431	19	0.0500	1.729	2.98334

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
Porfimer Sodium Assay
Temperature: 30 Degrees Centigrade

Time	_910001	_910004	_920005
0	104.40	99.55	106.75
1	104.60	97.70	104.10
3	97.00	97.90	96.15
6	97.00	96.60	98.20
9	.	95.30	98.65
12	99.60	99.55	102.25
15	.	93.95	98.50
18	.	98.45	102.85
21	97.60	.	.
24	95.45	.	.

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
Porfimer Sodium Assay
Temperature: 30 Degrees Centigrade

SOURCE	SS	DF	MS	F	P
A	59.11	4	14.78	1.59653	0.22078
B	51.79	2	25.90	2.79786	0.08904
C	7.32	2	3.66	0.39519	0.67958
D	157.35	17	9.26	.	.
E	226528.24	6	37754.71	.	.

```
**************************************************************
* Statistical Analysis:                                      *
*      Key to sources of variation                           *
* A = sep. intercep, sep slope | com intercep, com slope      *
* B = sep. intercep, com slope | com intercep, com slope      *
* C = sep. intercep, sep slope | sep intercep, com slope      *
* D = Residual                                               *
* E = Full Model                                             *
**************************************************************
```

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
Porfimer Sodium Assay
Temperature: 30 Degrees Centigrade
95% One-Sided Lower Confidence Limit

Separate Intercepts and Common Slope

BATCH	ESTIMATED DATING PERIOD (MONTH)
#910001	37
#910004	29
#920005	40

Stability Analysis
Sponsor: QLT Phototherapeutics Inc
NDA 20-451 Photofrin
Package: 75 mg/vial
Porfimer Sodium Assay
Temperature: 30 Degrees Centigrade

Accumulated Changes at Proposed Shelf-Life From Initial Values

Slop Estimation	Slop Std. Err.	Mean Square Error	Degrees of Freedom	One Tailed Probalility	Critical Point	Accumulated Change
-0.17492	0.085639	8.66679	19	0.0500	1.729	-8.89421

Clin. Pharm
+ Bio

DEC 19 1995

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-451/AZ **Submission Date:** December 04, 1995

Drug Name, Dose and Formulation: Porfimer Sodium, 2 mg/kg, Sterilized freeze-dried powder (75 mg)

Sponsor: QLT Phototherapeutics, Vancouver, British Columbia, Canada V5Z4H5

Reviewer: N.A.M. Atiqur Rahman

Type of Submission: New Drug Application

Drug Classification: 1P

The current submission includes revised package insert for Photofrin. The sponsor preferred to retain their original pharmacokinetic section of the package insert based on response 2. of the Pharmacology, Toxicology, Biopharmaceutics Section of faxed letter dated November 28, 1995 (Appendix). The sponsor was concerned about the possibility that physicians may attempt to give a second dose too early if the half-life is stated as such, and as a result patients may suffer adverse consequences. In the Dosage and Administration section it is clearly stated that "Patients may receive a second course of PDT a **mininum of 30 days** after the initial therapy; up to three courses of PDT (each separated by a **minimum of 30 days**) can be given. Therefore, the physicians should not administer a second course before 30 days.

The sponsor was suggested to accept the Division of Pharmaceutical Evaluation I revised Pharmacokinetic section of the Package Insert via fax dated December 08, 1995.

COMMENTS:

1. The following should be substituted for the Pharmacokinetics subsection of the Clinical Pharmacology section:

" Following a 2 mg/kg dose of Porfimer sodium to 4 male cancer patients, the average peak

plasma concentration was 15 ± 3 μg/mL, the elimination half-life was 250 ± 285 hour, the steady-state volume of distribution was L/kg, and the total plasma clearance was mL/min/kg. The mean plasma concentration at 48 hour was 2.6 ± 0.4 μg/mL.

Photofrin was approximately 90% bound to serum protein, studied *in vitro*. The binding was independent over the concentration range of μg/mL.

The influence of impaired hepatic function on Photofrin disposition has not been evaluated."

RECOMMENDATION:

The comment should be conveyed to the sponsor.

N.A.M. Atiqur Rahman 12/14/95

N.A.M. Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

FT: Initialed by Mehul U. Mehta, Ph.D. MUM 12/19/95

cc: NDA 20-451
HFD-150/ Div File
HFD-150/ Medical Officer
HFD-150/ JJohnson
HFD-150/CSO (Zimmerman)
HFD-340 (Vishwanathan)
HFD-860 (Malinowski, Mehta, Rahman)
HFD-870 (LChen)
HFD-880 (Fleischer)
HFD-860/ Biopharm Drug, Chron, and Reviewer's files

JUN 27 1995

NDA: 20-451/BB **Submission Date:** June 21,1995

Drug Name, Dose and Formulation: Porfimer Sodium, 2 mg/kg, Sterilized freeze-dried powder (75 mg)

Sponsor: QLT Phototherapeutics, Vancouver, British Columbia, Canada V5Z4H5

Reviewer: N.A.M. Atiqur Rahman

Type of Submission: New Drug Application

Drug Classification: 1P

The submission includes responses to the Biopharmaceutics deficiencies for Photofrin NDA 20-451. The responses are presented in the **appendix.** The sponsor has agreed with the Agency that additional pharmacokinetic characterization of Photofrin is required in patients following more than one course of therapy in targeted population, and in hepatic impaired patients, and in females. The sponsor would like to commit to conducting Phase IV pharmacokinetic studies post-approval and would like to discuss the details of such studies with the Agency.

As mentioned in the original NDA review, the pharmacokinetic parameter estimates from Pharmacokinetic Report No. 4 (Japanese Study) should be used for Pharmacokinetic Section of the Package Insert in the interim.

The sponsor has mentioned that high doses of ^{14}C-Photofrin will be required to follow the disposition of the drug for several weeks, and it will be unethical to administer such high doses of radioactivity to humans. The sponsor should consider administering the maximum allowable dose of radioactive Photofrin, and study the disposition of the drug as long as the radioactivity counts are above the background.

COMMENTS

1. The following studies should be performed by the sponsor as Phase IV commitments to the Agency :

a. The sponsor should characterize the pharmacokinetics of Photofrin in both male and female patients with validated assay methodology. This study will provide information not only of any possible gender difference but also the overall descriptive pharmacokinetics of the drug in humans at the targeted dose.

b. The sponsor should determine the pharmacokinetics of Photofrin in patients with hepatic impairment. The study will help suggesting any adjustment for dosing in this population if required. Comm

2. The sponsor is highly recommended to characterize the mass balance of Photofrin using maximum allowable radioactive dose of the drug and monitoring for as long as the radioactivity counts remain above background.

RECOMMENDATION

The comments should be conveyed to the sponsor and issues raised in comments should be satisfactorily addressed by considering appropriate Phase IV studies.

N.A.M. Atiqur Rahman 06/27/95

N.A.M. Atiqur Rahman, Ph.D.

Pharmacokinetic Evaluation Branch I

First Draft Prepared on 06/22/95

Final Draft Prepared on 06/27/95

FT Initialed by Mehul U. Mehta, Ph.D. 6/27/95

cc: NDA 20-451 (orig), HFD-150, HFD-150 (CSO), HFD-426 (Mehta, Fleischer, MChen, Rahman), HFD-340 (Viswanathan), HFD-19 (FOI), Chron, Drug, and Reviewer's files.

APPENDIX I

NDA 20-451: PHOTOFRIN® porfimer sodium
RESPONSE TO BIOPHARM QUESTIONS OF DECEMBER 7, 1994

Question 1:

The formal study (D73 P503) conducted by the sponsor to evaluate the pharmacokinetics of PHOTOFRIN® was unacceptable because it failed to:

a) take into account the endogenous levels of porphyrins present in blood prior to drug administration,
b) assess the pharmacokinetics of PHOTOFRIN® alone, without the monomeric prophyrins, and
c) provide baseline chromatograms for review.

Response to Question 1:

a) In Study D73 P503, porfimer equivalents were measured in the pre-dose plasma samples. Results for 7 of the 12 patients were reported in the analytical method appendix (NDA Volume 31, pp 349 - 352, reproduced in Attachment 1) and the results from the remaining 5 patients were requested from the analytical laboratory and are also included in Attachment 1. The concentrations for all patients but one (Patient were found to be less than mcg/mL, i.e., below the reliable limit of quantitation. Thus, no endogenous porphyrins were present prior to the dose. Additionally, negligible fluorescence was found in the blank plasma samples used to generate the calibration curves.

b) The calibration curves were corrected for the fluorescence estimated to be due to monomers. Details (NDA Volume 31, pages 334, 336 and 342) are reproduced in Attachment 2.

c) Baseline chromatograms are not available since the samples were analyzed by a non-chromatographic (fluorescence) method.

For a drug like PHOTOFRIN®, beyond the general question of time to drug clearance, the value of plasma concentration data is limited. Plasma data are not predictive of tissue localization and play no role in determination of light dose or time of light administration. The estimates of plasma clearance and elimination half-life based on this 12 patient study are probably adequate for the use of PHOTOFRIN® in this orphan indication. However, we agree with the Agency that additional pharmacokinetic characterization would be helpful and we feel that the most useful information would come from evaluation of the following:

a) Pharmacokinetic parameters following more than one course of therapy, as our label will allow up to 3 courses; and

b) Pharmacokinetic parameters in patients with hepatic impairment, as

suggested by the Agency in Question 4.

We commit to conducting a Phase IV pharmacokinetic study post-approval and we would like to discuss the details of such a study with the Agency.

Question 2:

The submission failed to provide any mass balance estimates of PHOTOFRIN's distribution and excretion in humans. In male rats, about 10% of the drug was excreted in bile over 48 hours. The sponsor should provide information regarding the overall distribution and excretion of the drug in humans.

Response to Question 2:

Firstly, while 10% of the drug was excreted as PHE in the bile of the rat over 48 hours, the recovery of PHOTOFRIN-related species (PHE + Hp + HVD + Pp) was much higher, i.e., 23% in both males and females. Table 4 of the Preclinical Report 222 (Vol 27, page 168) is reproduced in Attachment 3.

With regard to overall distribution and excretion in humans, mass balance studies are not considered feasible for the following reasons:

1. The prolonged retention of PHOTOFRIN excludes the use of radioactive tracers such as ^{99}Technicium ($T_{1/2}$ = 6 hours) and ^{111}Indium ($T_{1/2}$ = 2.81 days), which have too short a half-life. Tritium labelling (by general exchange) is very unreliable. It is considered unethical to give ^{14}C-PHOTOFRIN in high enough doses to allow the drug to be followed for several weeks.

2. As we have learned from animal studies, most of the dose is eliminated in the feces. Although the methodology for detecting some of the porphyrins in human feces exists (it was developed for the diagnosis of porphyrias), it is very unlikely that non-radiotracer methods would be sufficiently sensitive to allow the whole dose to be traced. The results could also be confounded by the action of bacterial flora in the intestinal tract, which are known to metabolize some of the porphyrins.

In the Japanese pharmacokinetic study (n = 4), no drug was detected in the urine (Amendment to NDA submitted May 24, 1994, replacement for Volume 32, page 332, reproduced in Attachment 3). This finding in humans is consistent with the animal studies in which elimination was principally via the liver.

Question 3:

The sponsor should evaluate the pharmacokinetics of PHOTOFRIN® in both male and female patients; no such information has been presented in this submission.

Response to Question 3:

Three of the 12 patients (25%) in pharmacokinetic study P503 were female (Patients As shown below, mean pharmacokinetic parameters were similar between males and females.

Group	AUCinf (mcg.hr/mL)	Cmax (mcg/mL)	Half-life (hours)
Males (n = 9): Mean (Range)	2855	82.5	551
Females (n = 3): Mean (Range)	2672	71.0	405

In the NDA, we analyzed efficacy by gender for esophageal cancer patients and found no differences. We also analyzed safety by gender for three different populations, patients with esophageal cancer, Once again, we found no differences by gender.

As indicated in the response to Question 1 above, we plan to conduct a Phase IV pharmacokinetic study and this study would include both males and females. In addition to standard analyses, the data will be presented by gender.

Question 4:

There were no studies or reports evaluating the pharmacokinetics of PHOTOFRIN in geriatric, in hepatic dysfunction, and in renal impaired patients. The sponsor should generate and provide this information to the Agency so that the quality of information in the package insert can be improved.

Response to Question 4:

Geriatric Patients:

The 12 patients for whom we have pharmacokinetic data from Study P503 ranged in age from years. The median age was 69. Eight of the 12 patients were older than 65 years.

For all three indications in which we have conducted clinical trials, most of the patients have been elderly. The median age of PDT-treated patients was 69 in the esophageal cancer trials, 66 in the lung cancer trials, and 67 in the bladder cancer trials. It is most likely that patients who will be treated with PHOTOFRIN postmarketing will also be elderly.

In the NDA, we have analyzed efficacy (esophageal cancer) and safety (all three indications) by patient age (younger than 60 years versus 60 years or older) and found no differences.

Patients with Hepatic Dysfunction:

We agree that this is an area in which we would like to collect more data. Two questions are of interest in patients with hepatic impairment.

1. What is the effect of PHOTOFRIN® on liver function in a patient who has pre-existing impairment?

2. What is the effect of liver impairment on the elimination of PHOTOFRIN®?

In response to the first question, we already have some information. A few patients with abnormal liver function, based on WHO grades for SGOT and SGPT > 0, were enrolled in the clinical studies. The results for PDT and control patients, across all programs (esophageal,) are summarized below (derived from NDA Volume 54, Appendix 19, pp. 190 - 209, all patients for whom both baseline and post-baseline data are available). The extent of changes following PDT were similar to control groups, regardless of initial WHO grade.

Changes in Liver Function by Baseline WHO Grade

Parameter = SGOT

Treatment	Baseline WHO Grade	Number of Patients					
		Total	Worsened	Degree Worsened			
				1 Grade	2 Grades	3 grades	4 Grades
PDT	Grade 0	261	42	30	9	3	0
	Grade 1	16	6	5	0	1	0
	Grade 2	2	0	-	-	-	-
	Grade 3	1	0	-	-	-	-
	Grade 4	0	0	-	-	-	
Control	Grade 0	[illegible]	31	22	6	1	2
	Grade 1	[illegible]	4	4	0	0	0
	Grade 2	[illegible]	0	-	-	-	-
	Grade 3	0	0	-	-	-	-
	Grade 4	0	0	-	-	-	-

Parameter = SGPT

Treatment	Baseline WHO Grade	Number of Patients				
		Total	Worsened	Degree Worsened		
				1 Grade	2 Grades	3 Grades
PDT	Grade 0	209	39	22	10	7
	Grade 1	11	2	1	1	0
	Grade 2	6	0	-	-	-
	Grade 3	1	0	-	-	-
	Grade 4	0	0	-	-	-
Control	Grade 0	164	25	19	5	1
	Grade 1	8	2	1	1	0
	Grade 2	0	0	-	-	-
	Grade 3	1	0	-	-	-
	Grade 4	0	0	-	-	-

To address the second question, i.e., elimination in patients with hepatic dysfunction, we wish to propose that, in addition to the pharmacokinetic study in non-compromised patients mentioned in Point 1 above, we also collect pharmacokinetic data in patients with liver impairment as a Phase IV commitment.

Patients with Renal Impairment:

There is no evidence that PHOTOFRIN is metabolized or cleared by the kidney to any significant extent. As mentioned in the response to Question 2 above, in the limited Japanese pharmacokinetic study, no drug was detected in the urine. In radiotracer studies in mice, rats and dogs, very little radioactivity was detected in the urine. Therefore, studies of the pharmacokinetics of PHOTOFRIN® in patients with renal impairment will probably not be helpful.

Mr. Zimmerman

NDA: 20-451 **Submission Date:** April 12, 1994

Drug Name, Dose and Formulation: Porfimer Sodium, 2 mg/kg, Sterilized freeze-dried powder (75 mg)

Sponsor: QLT Phototherapeutics, Vancouver, British Columbia, Canada V5Z4H5

Reviewer: N.A.M. Atiqur Rahman

Type of Submission: New Drug Application

Drug Classification: 1P

SYNOPSIS

Photofrin porfimer sodium is a porphyrin-derived photosensitizing agent used in the photodynamic therapy (PDT) for the reduction of obstruction and palliation of dysphagia in patients with completely or partially obstructing esophageal cancer. Photodynamic therapy with photofrin is a two-stage process requiring administration of both drug and light. The first stage of PDT is the intravenous injection of photofrin at 2 mg/kg over 3 to 5 minutes. Illumination of laser light at 630 nm wavelength within 40-50 hours following injection with photofrin constitutes the second stage of therapy.

The pivotal pharmacokinetic study D73-P503 which included 12 cancer patients (9 males, 3 females) failed to properly assess the pharmacokinetics of photofrin in plasma. The assay methodology used in the study was non-specific, and it failed to distinguish various porphyrin related blood components in quantification of photofrin. In the same study, the baseline levels of photofrin was also not evaluated. Supporting pharmacokinetic study (Report No: 4) quantitated photofrin by two different analytical methods; direct fluorescence detection and HPLC separation followed by fluorescence detection. The two methods derived similar pharmacokinetic parameters values; however, elimination half-life estimation by these two methods were different. The study included four cancer patients, and it showed average plasma concentration of 2.6 $\pm$ 0.4 μg/mL at 48 hour; the approximate timing for laser therapy. The total plasma clearance of the drug was low mL/h/kg), and the elimination half-life was approximately 250 $\pm$ 285 hour. The drug was 90% bound to plasma proteins at concentrations of μg/mL. The submission did not provide any information on the comparative pharmacokinetics of photofrin in male and female patients, and in special populations (geriatric, renal or hepatic impaired, etc.). There was no drug interaction study performed. Mass balance study of photofrin was not included in the submission.

TABLE OF CONTENTS

Selected Abbreviations

PDT	Photodynamic therapy
HPLC	High performance liquid chromatography
KS	Karnofsky Performance Status
PK	Pharmacokinetics

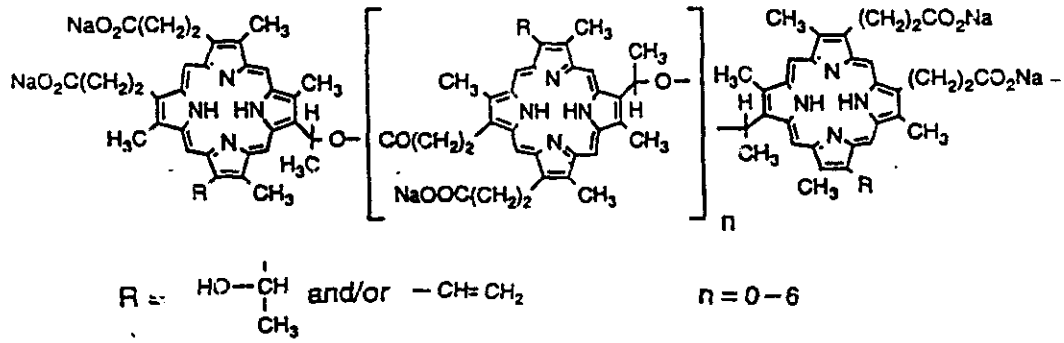
C_{max}	Maximum plasma concentration
AUC	Area under the curve
CLT	Total plasma clearance
V_{ss}	Steady-state volume of distribution
$t_{1/2}$	Elimination half-life
HP	Hematoporphyrin
HVD	Hydroxyethylvinyl deuteroporphyrin
PP	Protoporphyrin
I.V.	Intravenous
Nd:YAG	Neodymium yttrium-aluminum-garnet
HDL	High density lipoprotein
LDL	Low density lipoprotein
VLDL	Very low density lipoprotein

BACKGROUND

PHYSICOCHEMICAL PROPERTIES:

Photofrin is not a single chemical entity; it is a mixture of oligomers formed by ether and ester linkages of up to eight porphyrin units. It also includes monomers like hematoporphyrin, hydroxyethylvinyldeuteroporphyrin and protoporphyrin. It is a dark red to reddish brown cake or powder which is soluble in water and methanol.

Photofrin Structure



INDICATIONS AND USAGE:

Photodynamic therapy with Photofrin is indicated for the reduction of obstruction and palliation of dysphagia with completely or partially obstructing esophageal cancer.

RECOMMENDED DOSAGE AND ADMINISTRATION:

Photodynamic therapy with Photofrin is a two-stage process requiring administration of both drug and light. The first stage of photodynamic therapy is the intravenous injection of Photofrin at 2 mg/kg. Illumination with laser light 40-50 hours following injection with Photofrin constitutes the second stage of therapy. A second laser light may be given. Patient may receive a second course of PDT a minimum of 30 days after the initial therapy; up to three courses of PDT (each separated by a minimum of 30 days) can be given. Before each course of treatment, patients should be evaluated for the presence of a tracheoesophageal or bronchoesophageal fistula.

FORMULATION

Photofrin II formulation was used in all pharmacokinetic studies. Photofrin II is the formulation that is proposed for marketing.

SUMMARY OF PHARMACOKINETIC STUDIES

a. Study in Bronchial Cancer Patients (Study No: D73-P503)

Patients: 12 (9 males, age 52-86, KS $\geq$50%) with non-small cell bronchogenic carcinoma

Dose: 2 mg/kg 3-5 minutes intravenous

Sampling: up to 8 weeks . 3 patients died before completion of sampling.

Analytical Method: Acid hydrolysis, followed by HPLC with fluorescence detection of the monomers at 490/590. Calibration curve from μg/mL. The assay to quantitate porfimer sodium failed to differentiate various porphyrins in the plasma.

PK parameters: C_{max} μg/mL, $AUC_{(0-\infty)}$ μg.hr/L, CLT L/hr/kg, V_{ss} L/kg, $t_{1/2}$ hrs(21.5 days).

b. Pharmacokinetics of Photofrin II in Man (Report No: 2)

Patients: 4 (patients history not available)

Dose: 2 mg/kg 3-5 minutes intravenous

Sampling: up to 48 hours.

Analytical Method: Alkaline hydrolysis, followed by HPLC with fluorescence detection of monomers at 400/615-630. Calibration curve concentration range unknown. The assay to quantitate porfimer sodium failed to differentiate various porphyrins in the plasma.

PK parameters: C_{max} μg/mL at hr, $t_{½}$ hrs, possibly distribution half-life.

Binding of porphyrin to plasma proteins and lipoproteins were determined.

c. Investigation of the in vivo dynamics of Porfimer Sodium after Intravenous Injection

(Report No: 4)

Patients: 4 (2 early lung cancer, 1 esophageal and 1 bladder cancer)

Dose: 2 mg/kg Infusion; duration : unknown.

Sampling: up to 168 hours.

Analytical Method: Quantitated dimers/oligomers from its related monomers (HP, HVD, and PP). Calibration curve concentration ranged from μg/mL.

PK parameters: C_{max} μg/mL , $AUC_{(0-\infty)}$ μg.hr/L, CLT mL/hr/kg, V_{ss} L/kg, $t_{½}$ hrs.

SERUM PROTEIN BINDING (Report No: 3)

Concentrations: μg/mL

Duration : minutes

Temperature: 37°C

Method: Ultracentrifugation, hours at

Percent bound: 90%

COMMENTS (Medical Officer)

1. In section "Photofrin Administration" on page 20 of the package insert, duration of intravenous injection of mg/kg body weight over minutes appears to be too rapid to administer mL volume in a patient. Should the duration of infusion be at least minutes ? However, the effects of rate of input on the pharmacokinetics and toxicity of the drug is not available for assessment.

2. In Dosage and Administration section, up to three courses of photodynamic therapy is suggested for evaluated eligible patients. Each course may be separated by a minimum of . days. The drug appears to have a long half-life of about hour. Dose adjustment may be necessary for subsequent courses to avoid potential accumulation, and to reduce toxicity of this photosensitive agent in the body.

3. Differences in the pharmacokinetics of photofrin in the elderly versus adults were not presented in this submission. The statement regarding the use in elderly patients on page 12 of package insert should be based on the clinical experience in this population.

COMMENTS (Package Insert)

1. The pharmacokinetic parameters and information obtained from study D73 P503 can not be properly validated due to lack of assay specificity. The data from PK Report No. 2 (Vol.32, p. 200) is also inconclusive due to lack of assay specificity and due to inadequate duration of sampling. The estimated pharmacokinetic parameters from PK Report No. 4 appears to be more reliable, since the HPLC assay methodology used in this study separated porfimer sodium from the other porphyrin related compounds in plasma. The study represented the pharmacokinetics of oligomers present in the drug product. Therefore, the data generated in this study should be used in the package insert in the interim. The sponsor should conduct properly designed pharmacokinetic studies, generate data, and submit for review.

The following statement may represent the Pharmacokinetic section of the Package Insert:

" Following a 2 mg/kg dose of porfimer sodium to 4 male cancer patients, the average peak plasma concentration was 15 ± 3 μg/mL, the elimination half-life was 250 ± 285 hour, the steady-state volume of distribution was L/kg, and the total plasma clearance was mL/min/kg. The mean plasma concentration at 48 hour was 2.6 ± 0.4 μg/mL."

2. The sponsor did not conduct any mass-balance study to substantiate the following statement in the Pharmacokinetic section of the package insert:

" Excretion of porfimer sodium components occurs primarily via the fecal route."

The statement is based on studies conducted in mouse, rat, and dog using doses different from the dose suggested for human use. The statement should be deleted.

3. There was no formal pharmacokinetic based drug interaction study performed by the sponsor. Therefore, on page 8, the drug interaction section should be evaluated based on the clinical observations only.

DEFICIENCIES

1. The formal study (D73 P503) conducted by the sponsor to evaluate the pharmacokinetics of photofrin was unacceptable because it failed to :

a) take into account the endogenous levels of porphyrins present in blood prior to drug administration,
b) assess the pharmacokinetics of photofrin alone, without the monomeric porphyrins. and
c) provide baseline chromatograms for review.

The pharmacokinetic parameter estimates of photofrin from Report No: 4 appear to be the most reliable assessment; however, the data derived from this study are highly qualitative since the study enrolled only 4 patients.

2. The submission failed to provide any mass balance estimates of photofrin's distribution and excretion in humans. In male rats, about 10% of the drug was excreted in bile over 48 hour. The sponsor should provide information regarding the overall distribution and excretion of the drug in humans.

3. The sponsor should evaluate the pharmacokinetics of photofrin in both male and female patients; no such information has been presented in this submission.

4. There were no studies or reports evaluating the pharmacokinetics of photofrin in geriatric, in hepatic dysfunction, and in renal impaired patients. The sponsor should generate and provide these information to the Agency for review so that the quality of information in the package insert can be improved.

RECOMMENDATION

The pharmacokinetics of photofrin presented in this submission is **not adequate** to meet the general requirements of the Division of Biopharmaceutics. The **deficiencies** should be conveyed to the sponsor.

N.A.M. Atiqur Rahman, Ph.D. 11/21/94
Pharmacokinetic Reviewer

First Draft Prepared on 07/06/94
Biopharm Day 09/06/94

FT Initialed by Mehul U. Mehta, Ph.D. 11/23/94

cc: NDA 20-451 (orig), HFD-150, HFD-150 (CSO), HFD-426 (Mehta, Fleischer, MChen, Rahman), HFD-340 (Viswanathan), HFD-19 (FOI), Chron, Drug, and Reviewer's file

APPENDIX I

SINGLE DOSE PHARMACOKINETIC STUDIES

I. REPORT NO: 4

INVESTIGATOR AND LOCATION:

Katsuo Aizawa
Harufumi Kato
Tokyo Medical College

Seishiro Mimura
Osaka Adult Disease Center

Tadao Uchibayashi
Kanazawa University Hospital

Hiromi Wada
Kyoto University Chest Disease Laboratory Hospital

Masataka Kitamura
Tomio Sasagi
Japan Laderle, Ltd.

OBJECTIVES:

This study was performed to determine the pharmacokinetics of porfimer sodium in humans. The measurement over time of the overall concentration of porphyrin in plasma in humans has been performed; however, there are no reports of quantitative measurement of isolated porfimer sodium which is the most effective species in killing tumor cells are available.

FORMULATION:

The Photofrin injection was freeze dried product containing mg of porfimer sodium per vial. The drug product was prepared according to the Manufacturing scheme The drug was dissolved in mL of a % glucose liquid to yield a mg/mL intravenous injection solution of porfimer sodium.

The study was conducted between February 1992- March 1992.

STUDY DESIGN:

According to Phase III clinical trial protocol, 2 mg/kg dose of porfimer sodium was administered intravenously to four patients who were not exposed to any prior therapy for various carcinoma. After 48 to 53 hours of drug administration, the site of the lesion was illuminated with 630 nm laser light using an excimer laser. A 2.5 mL of blood sample was drawn prior to and after 1, 3, 9, 24, 48, 72, 120 and 168 hours of drug administration. Plasma was separated at once and preserved at -20°C until analysis. Urine samples were designed to be collected at 24 hour intervals up to 168 hours after medication; however, urine could not be collected from two patients.

ASSAY METHODOLOGY:

High performance liquid chromatographic method with fluorescence detection was used to isolate and quantitatively measure porfimer sodium and each of the related substance in plasma and urine. The method of acidic and basic hydrolysis of porfimer sodium used in other studies failed to separately estimate the pharmacokinetics of porfimer sodium and other plasma related porphyrins. A methanolic extraction of plasma and urine was performed. Porfimer and other related compounds were separated on a reverse phase TSKgel ODS-80TM column using HPLC method. The peak areas for each substance was measured by fluorescence detector at an excitation wavelength of 400 nm and an emission wavelength of 630 nm. The recovery rate of

porfimer sodium in plasma was about 57% and in urine about 93%. A calibration curve with concentration ranging from μg/mL was used for plasma measurements and from μg/mL for urine measurements. The detection limits for porfimer sodium and other major porphyrin related components, hematoporphyrin (HP), hydroxyethylvinyldeuteroporphyrin (HVD) and protoporphyrin (PP) in plasma were 1.4 , 0.2, 0.2, and 0.5 μg/mL, respectively. The detection limits in urine for porfimer sodium, Hp, HVD, and Pp were 2.0, 0.1, 0.2, and 0.5 μg/mL, respectively. The intra- and inter- assay variability were not reported in the submission. The detailed assay methodology is presented in the **appendix.**

DATA ANALYSIS:

The study evaluated peak plasma concentration (C_{max}), distribution half-life ($t_{½(\alpha)}$), elimination half-life ($t_{½(\beta)}$), area under the curve (AUC), clearance (CL) and volume of distribution (V_{ss}) of porfimer sodium; however, the method of analysis was not provided.

RESULTS:

The plasma concentration of porfimer sodium declined in a biphasic manner with distribution half-life ranging between hours, and elimination half-life ranging between hours. The clearance of the drug was mL/min/kg and steady state volume of distribution was L/kg. The detailed pharmacokinetic parameter estimates are presented in **Table No: 1.** There was no photofrin detected in the urine samples.

CONCLUSIONS:

1. The drug porfimer sodium appears to have a very low clearance and a long elimination half-life. The plasma concentration at hour is when the laser therapy is proposed to be administered. There is high variability in the elimination half-life (CV 114%) and AUC (CV 73%) estimates.

TABLE 1 Pharmacokinetic parameters of porfimer sodium

Parameter	Patient No:	Patient No:	Patient No:	Patient No:	Mean ± SD
Cmax (μg/mL)					15.3 ± 2.98
$t_{½(\alpha)}$ (hr)					7.7 ± 2.49
$t_{½(\beta)}$ (hr)					250 ± 285
AUC (μg.hr/mL)					974 ± 710
CL (mL/h/kg)					3.05 ± 2.1
V_{ss} (L/kg)					0.49 ± 0.28

2. The plasma samples in this study were analyzed by two separate analytical methodology (fluorescence assay and HPLC combined with fluorescence detection). The HPLC assay was able to separate the drug entity from other porphyrins monomers in the blood. The pharmacokinetic parameters derived using this assay appears to be more reliable.

II. STUDY NO: D73P503

STUDY TITLE:

A randomized phase III comparative study of the safety and efficacy of photodynamic therapy (PDT) utilizing PHOTOFRIN II (polyporphyrin) versus thermal ablation therapy using the Nd:YAG laser for obstructing or partially obstructing bronchogenic carcinoma. Pharmacokinetic Study.

INVESTIGATOR AND LOCATION:

Dr. M. Leroy, Centre Medico-Chirugical Foch Suresnes, Cedex, France

Prof. P. Spinelli, Instituto Nazionale Tumori, Milan, Italy

Dr. J.P. Diaz Jimenez, Clinical Tres Torres, Barcelona, Spain

Mr. K. Moghissi, Castle Hill Hospital, Cittingham, Hull, United Kingdom

Dr. K. Hauessinger, Zentral Krankenhause der LVA Bayern Gauting, Bayern, Germany

Prof. K. Gierckosky, Radiumhospitalet, 0310 Montebello, Oslo, Norway

OBJECTIVES:

The objectives of the randomized protocol D73 P503 were to evaluate and compare the safety and efficacy of photodynamic therapy (PDT) employing PHOTOFRIN II and controlled uniform laser light of 630 nm with that of thermal ablation therapy with the Neodymium yttrium-aluminum-garnet (Nd:YAG) laser in the treatment of obstructing o. partially-obstructing

bronchogenic carcinoma.

The objective of the pharmacokinetic study was to estimate the pharmacokinetic characteristics of PHOTOFRIN II in a subset of randomized patients and additional non-randomized patients who were treated with PDT in Protocol D73 P503 (Amendments 4 and 5).

FORMULATION:

The Photofrin injection was freeze dried product containing mg of porfimer sodium per vial. The drug was dissolved in mL of a % dextrose solution to yield a mg/mL intravenous injection solution of porfimer sodium. Please see **appendix** for detailed report on formulation numbers and date of treatment.

Note: Three patients' treatment were not documented with the batch number. The information regarding the Manufacturing scheme followed to prepare the drug product used in this trial is not available.

Study Duration: June, 1991 - January, 1992.

STUDY DESIGN:

The D73 P503 comparative study was a randomized, controlled, multicenter trial. The pharmacokinetic addition was designed as an open label, multicenter, non-comparative, single course study to estimate the pharmacokinetic profile of Photofrin in a subset of 12 (9 male/3 female) bronchogenic carcinoma patients treated in the D73 P503 protocol.

The total treatment duration ranged from a minimum of 5 days to a maximum of 9 days. Day 1 was for the I.V. injection over 3-5 minutes. Day 3 was the first application of laser light. Day 5 or Day 6 was for the debridement of necrotic tissue from the first laser treatment, and could include an optional second light application. An optional second debridement of necrotic

tissue could occur on Days 7-9.

Table representing the sampling schedule is presented in the **appendix.** At each time point, 10 mL blood was taken and stored in a Lithium/Heparin tube. The sample was immediately centrifuged at g for minutes, and the plasma was aliquoted into polypropylene ampoules and frozen at -20° to -40°C.

ASSAY METHODOLOGY:

The plasma samples were analyzed in the

The principle of the analytical method used in this study is based on the fact that when treated with 1M HCl at 100°C for about 10 minutes, the oligomer fraction which is less fluorescent, is partially converted to monomeric porphyrins, which fluoresce strongly. The porphyrins in plasma were first extracted with a mixture of ethyl acetate and glacial acetic acid (4:1 v/v). The supernatant was separated and treated with 1M HCl to convert the oligomer porfimer into monomeric porphyrins. The acid phase was neutralized with % sodium acetate and the porphyrins were extracted into ethyl acetate. The residue from the extract was dissolved in µL of methanol containing µL of 1M hydrochloric acid, and µL sample was injected onto a Waters C_{18} Novapak column with a linear gradient from % methanol: % ammonium acetate buffer %, pH 5.16) to % menthol over minutes at a flow rate of 1 mL per minute. The porphyrins were detected by their absorbance at nm and fluorescence emission at nm. The detailed assay methodology is presented in the **appendix.**

DATA ANALYSIS:

Overall, 12 patients were enrolled in this study. Patients died 27, 38, and 54 days, respectively, after dosing. However, pharmacokinetic analysis was performed on data from all 12 patients who received photofrin treatment.

The peak plasma concentration (C_{max}) was determined from the plasma concentration-time profiles of each patient. The terminal slope (K) was determined by best fit least-squares regression analysis of the terminal log-linear portion of the log plasma concentration versus time profile. The elimination half-life was calculated as the quotient /K. The area under the plasma concentration versus time curve (AUC_{0-t}) from time zero to time of the last reportable drug concentration (C_t) was determined by using the linear trapezoidal rule up to C_{max}, followed by the log trapezoidal method at subsequent times. AUC from time zero to infinity ($AUC_{0-\infty}$) was estimated by the sum of AUC_{0-t} and C_t/K.

The total systemic clearance (CL) and volume of distribution (Vd_{ss}) at steady-state was calculated using the following equations:

$$CL = \frac{Dose}{AUC_{(0-\infty)}}$$

$$V_{ss} = \frac{Dose \cdot AUMC}{(AUC)^2} - \frac{Dose \cdot T}{AUC \cdot 2}$$

where T is the time of infusion, and AUMC is the area under the moment curve.

RESULTS:

The semilogarithmic plot of mean plasma concentrations versus time in 12 patients indicated a biexponential profile of photofrin in humans. The mean peak plasma concentration attained between 5 to 15 minutes was 79.6 μg/mL. The drug showed a long elimination half life of hour. The volume of distribution and clearance of the drug were L/kg and mL/h/kg, respectively.

Table 2 Pharmacokinetic parameter estimates of photofrin

Parameters (units)	Mean ± SD
C_{max} ($\mu g/mL$)	79.6 ± 48.2
$AUC_{(0-\infty)}$ ($\mu g.h/mL$)	2810 ± 1124
CL (mL/h/kg)	0.84 ± 0.42
$t_{1/2}$ (hr)	515 ± 136
V_{SS} (L/kg)	0.42 ± 0.33

N=12

CONCLUSIONS:

1. The pre-drug blood samples were not analyzed to determine the baseline levels of porphyrin monomers in blood. The assessment appears to be necessary to distinguish between endogenous levels of porphyrins and the estimated levels at the later sampling time. This will affect the elimination-half life estimation for photofrin.

2. The drug appeared to have a long elimination half-life and a slow clearance in patients.

III. REPORT NO: 2

TITLE:

Pharmacokinetics of PHOTOFRIN II Distribution in Man. Kessel[1], D., Nseyo[2], U., Schultz[1], V., and Sykes[3], E. SPIE, 1426. Optical Methods for Tumor Treatment and Early Diagnosis: Mechanisms and Techniques (1991).

[1]Department of Pharmacology, Wayne State University, School of Medicine, Detroit, MI; [2]Department of Urology, VA Hospital, Martinez, CA; [3]Department of Pathology, William Beaumont Hospital, Royal Oak, MI.

OBJECTIVES:

The objective of the study was to determine the plasma and blood component (HDL, LDL, and Albumin) pharmacokinetics of Photofrin II in patients.

SUMMARY OF THE REPORT:

In this study, plasma samples (0.5 to 48 hours) were obtained from four patients after administration of 2 mg/kg Photofrin II. Total porphyrin was estimated after base hydrolysis along with porphyrin distribution among protein, HDL, LDL, and VLDL fractions. HPLC studies were carried out to determine which Photofrin II components were associated with plasma. The study reported an initial plasma levels of approximately μg/mL of porphyrin maintained for at least 1 hour. The initial half-life of elimination was hour. Highest porphyrin levels were found in the HDL fraction before 48 hour.

Please see **appendix** for detailed report.

CONCLUSIONS:

1. The duration of plasma sampling was too short, for the assessment of various pharmacokinetic parameters of photofrin.

2. The assay failed to differentiate between photofrin and other porphyrin related components in plasma.

APPENDIX II

REPORT NO: 4

Test Methodology

1. Subjects

During the period from July 1990 to May 1992, medical examinations were conducted at

and, of the patients who were registered in the third phase clinical test[I,II,III] of photofrin (intravenous injection porfimer sodium formulation) for solid cancer, four patients in whom it was possible to study in vivo dynamics were selected as subjects for this test. An overview of the subjects is shown in Table 1.

Table 1. Subject Overview

Subject Number	Initials	Sex	Age (yrs)	Weight (kg)	Disease	PS	Prior Treat.
	.	M	83	50	Endoscopic early lung cancer	2	None
	.	M	63	62	Bladder cancer	0	None
	.	M	73	42	Endoscopic early lung cancer	1	None
	.	M	73	54	Esophagus cancer	0	None

PS: Performance status

2. Test Medicine

The photofrin injection was a freeze dried medicine containing mg of porfimer sodium in one vial. The photofrin injection was dissolved in ml of a % glucose liquid at the time of use and was used as a mg/ml intravenous injection solution of porfimer sodium.

PO# 326330

Data Concerning Measurement of Porfimer Sodium Concentration in Blood Plasma and Urine

Tests Conducted at:

Persons in Charge and Responsible for Tests:

Period Tests Conducted: February 26, 1991 through May 20, 1992
Test Conditions: 25°, 50%RH

Data Concerning Measurement of Porfimer Sodium Concentration in Blood Plasma and Urine

In order to study the dynamics of medication in the blood and urine when an individual is given a dosage of porphyrin, investigations were conducted using a fluorescent luminescence method and a high performance liquid chromatograph method (HPLC method) as measurement methods. The analyzed results at the time of determining the test methods and the results of the measurement of porfimer sodium concentration in blood plasma and urine when doses of photofrin were actually given to cancer patients are reported below.

I. Fluorescent Luminescence Method

In the fluorescent luminescence method, starting with porfimer sodium and three kinds of related substances, from the measurement of a comparison with the degree of luminescence of ingredients possessing similar structures included in the blood plasma or the urine, the measurement value records the overall concentration of porphyrin. Actually, the measurement value is indicated by the converted porfimer sodium concentration.

1. Measurement of Porfimer Sodium Concentration.

1) Method.

(1) Derivation of Calibration Curves.

Porfimer sodium is dissolved in a phosphate buffer (pH 7.4) and the solution is prepared with the porfimer sodium at about mg/ml. ml of this liquid is accurately measured and diluted blood plasma (blank blood plasma which is diluted times with phosphate buffer (pH 7.4)) is added to make precisely ml. ml of this liquid is accurately measured out and diluted blood plasma is added to make precisely ml μg/ml standard solution; this is equivalent to a concentration of μg/ml of porfimer sodium in blood plasma). With the same operations, standard solutions with concentrations of μg/ml μg/ml in blood plasma) are prepared. After the standard solution is incubated at 37° for three hours, the degree of fluorescence is measured at an excitation wavelength of nm and a fluorescent wavelength of nm and the calibration curves are derived.

(2) Treatment of Specimen.

Phosphate buffer (pH 7.4) is added to ml of the specimen to make precisely ml and this becomes the test sample liquid. Measurement of the degree of fluorescence of the test sample

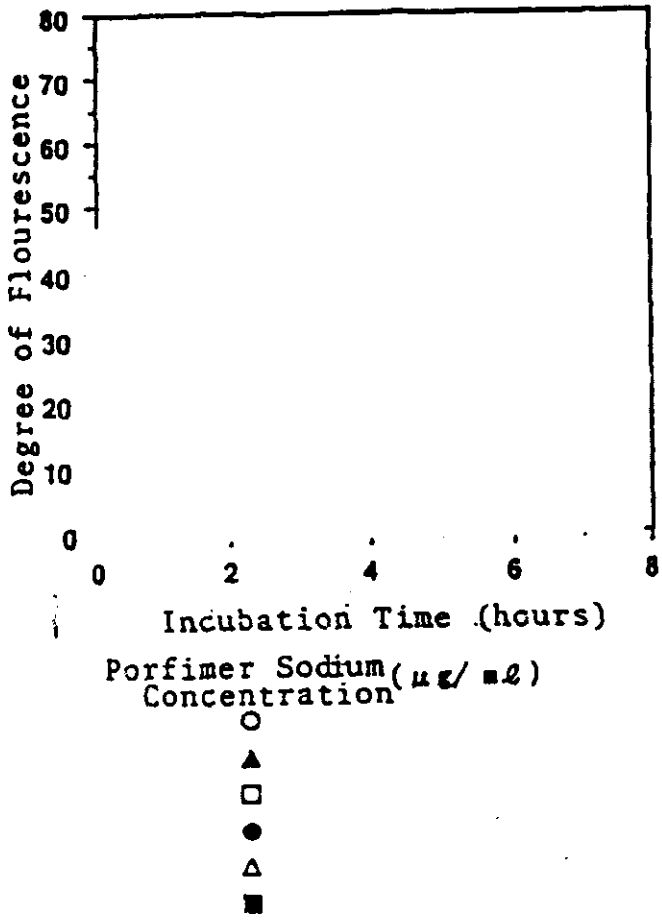


Figure 1. Change over time in flourescence depending on incubation of standard solution

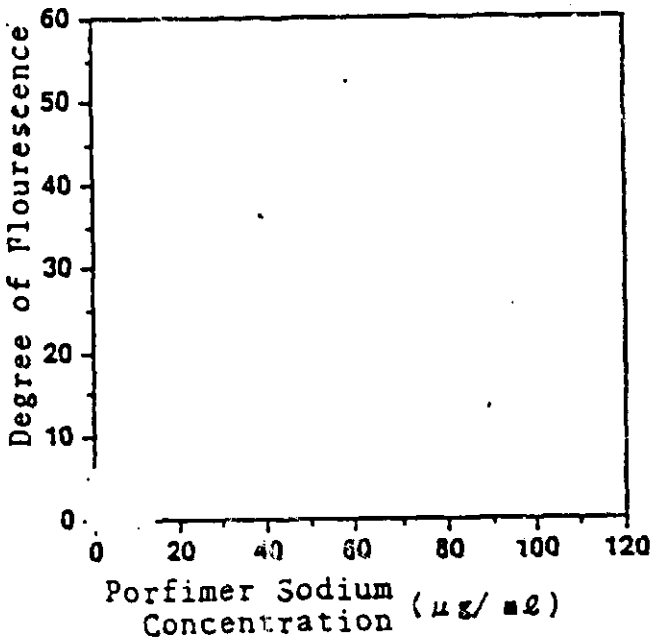


Figure 2. Derivation of graph line based on flourescent luminescence method

liquid at an excitation wavelength of nm and a fluorescent wavelength of nm is made.

2) Results.

(1) With respect to the blood plasma protein, the porfimer sodium indicates a high rate of protein bonding. Since the changes in the degree of fluorescence which indicates the porfimer sodium are forecast dependent on the degree of protein bonding, matters concerning these effects were investigated.

Porfimer sodium was added to the blood plasma and a liquid with a concentration of from μg/ml was produced as a test sample liquid and incubated at 37°. Measurements of the degree of fluorescence were taken periodically and the changes were examined. The results are shown in figure 1. For all of the concentrations the degree of fluorescence became stable at around three hours. It is regarded that this fact indicates that the bonding of the porfimer sodium and the blood plasma protein rises for a period and then becomes stable after about three hours. Following the above, incubation for three hours at 37° was conducted at the step of production of a standard liquid with concentrations of from μg/ml and, afterward, measurement of the degree of fluorescence was made at the calibration curves that were derived.

The calibration curves are shown in figure 2. Calculated in terms of the concentration of porfimer sodium in the blood plasma, in the range of from g/ml an excellent straight line with a correlation coefficient of was identified. Also, the detection limit of concentration in this method was μg/ml.

(2) Measurement of Concentration in the Blood Plasma of Patients.

The profiles of four cancer patients who were test subjects are shown in table 1 and the measurement results are shown in table 2. All of the patients were given porfimer sodium doses of 2 mg/kg.

Table 1. Patient Profiles

Item				
Sex	Male	Male	Male	Male
Age(years)	83	63	73	73
Weight(kg)	50	62	42	54
Disease name	Endoscopic early lung cancer	Bladder cancer	Endoscopic early lung cancer	Esophagus cancer

Table 2. Overall Concentration of Porphyrin in the Blood Plasma of Patients (Fluorescent Luminescence Method)

Units: μg/ml

After Dosage (hours)	Subject (initials)				Average
Predose	ND	ND	ND	ND	
1					
3					
9					
24					
48					
72					
120	ND	ND	ND	ND	
168	-	ND	ND	ND	
$\alpha T_{\frac{1}{2}}$(hr)					7.0
$\beta T_{\frac{1}{2}}$(hr)					59.9
AUC					771.2

ND Less than concentration detection limit μg/ml)
\- No specimen

2. Measurement of the Concentration of Porfimer Sodium in Urine.

1) Method.

(1) Derivation of Calibration Curves.

Porfimer sodium is dissolved in a phosphate buffer (pH 7.4) and the solution is prepared with the porfimer sodium at about mg/ml. ml of this liquid is accurately measured out and diluted urine (blank urine which is diluted times with phosphate buffer (pH 7.4)) is added to make precisely ml. ml of this liquid is measured out and diluted urine is added to make precisely ml μg/ml standard liquid; equivalent to a concentration of μg/ml of porfimer sodium in urine). Using the same operations, μg/ml concentrations of standard liquids μg/ml in urine) are prepared. The degree of fluorescence is measured at an excitation wavelength of um and a fluorescent wavelength of nm and the calibration curves are derived.

(2) Treatment of Specimen.

Phosphate buffer (pH 7.4) is added to ml of the specimen to make precisely ml and this becomes the test sample liquid. Measurement of the degree of fluorescence of the test sample liquid at an excitation wavelength of nm and a fluorescent wavelength of nm is made.

2) Results.

[(1)] The calibration curve derived by this method is shown in figure 3. Calculated in terms of the concentration of porfimer sodium in the urine in the range of from µg/ml, an excellent straight line with a correlation coefficient of was identified. Also, the detection limit of concentration in this method was µg/ml.

(2) Measurement of Concentration in Patient Urine.

The results of the measurements on two of the four previously mentioned subjects are shown in table 3.

Table 3. Overall Concentration of Porphyrin in Patient Urine (Degree of Fluorescent Luminescence)

Units: µg/ml

Accumulated Urine	Subject (initials)	
First Day	ND	ND
Second Day	ND	ND
Third Day	ND	ND
Fourth Day	ND	ND
Fifth Day	ND	ND
Sixth Day	-	ND
Seventh Day	ND	ND

ND Less than concentration detection limit µg/ml)
- No specimen

II HPLC Method

1. Measurement of Porfimer Sodium Concentration in Blood Plasma.

1) Method.

(1) Derivation of Calibration Curves.

Porfimer sodium is dissolved in a phosphate buffer (pH 7.4) and the solution is prepared with the porfimer sodium at about mg/ml. This liquid is successively diluted to precisely half strength and solutions from μg/ml are prepared. ml of these liquids are measured out and ml of blood plasma is added to each and standard liquids from μg/ml are made. After incubating the standard liquids for three hours at 37°, ml of methanol is added to ml of these liquids. After stirring for seconds and conducting ultra sound treatment for minute, centrifugal separation is done with revolutions for minutes and μl of the upper layer is poured into the HPLC and the calibration curves are derived.

(2) Treatment of Specimen.

ml of methanol is added to ml of the specimen and after stirring for seconds and conducting ultra sound treatment for minute, centrifugal separation is done with revolutions for minutes and μl of the upper layer is poured into the HPLC.

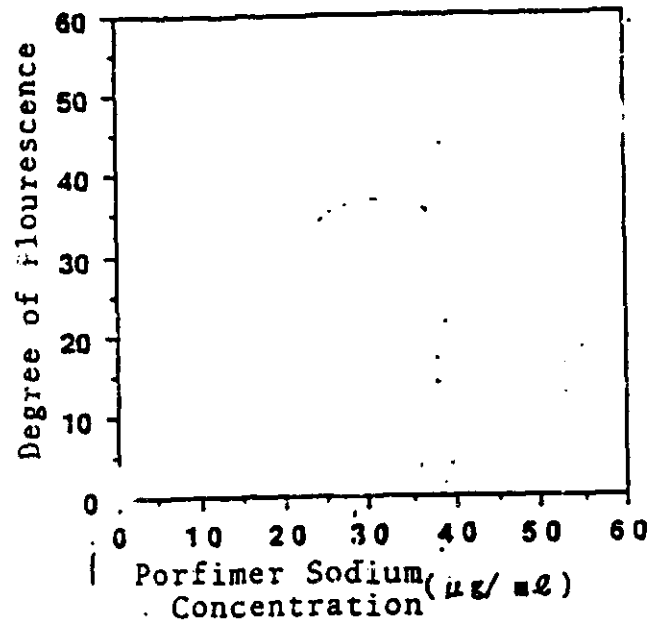


Figure 3. Derivation of graph line based on flourescent luminescence method

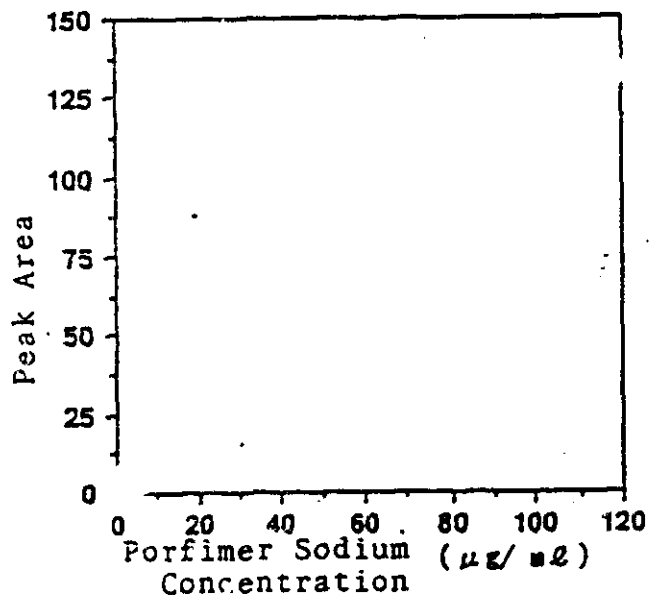


Figure 4. Derivation of graph line based on HPLC method

(3) HPLC Conditions.

The below conditions were instituted.

Items	Conditions		
Detector	Fluorescent luminescence meter (excitation wavelength: nm; fluorescent wavelength: nm)		
Column	A stainless steel tube with an inner diameter about mm, length about cm, which is filled with μm octadecylsilil silica gel for liquid chromatography. (TSK gel ODS-80Tm, 4.6 X mm)		
Column Temp.	Temperature regulated in the area of 45°		
Shift Phase	(A) Diluted sodium hydroxide test liquid is added to a mixture of water, methanol, tetrahydrofuran and glacial acetic acid and adjusted to a pH of 5.0 to 5.1. (B) Mixture of tetrahydrofuran and water		
Gradient Program	Analysis Time	Shift Phase (A)	Shift Phase (B)
	min. (until protoporphyrin peak completely elutes)	100%	0%
	min.	Linear gradient	
	min. (until porfimer sodium peak completely elutes)	0%	100%
	min.	Linear gradient	
	min.	100%	0%

2) Results.

(1) The derived calibration curve, calculated in terms of the concentration in the blood plasma in the range of from μg/ml, was identified as an excellent straight line with a correlation coefficient of (figure 4). Also, the average recovery rate of porfimer sodium after the deproteinization operation in the concentration range was %. The concentration detection limit of porfimer sodium was ng/ml and the concentration detection limits of the three main kinds of

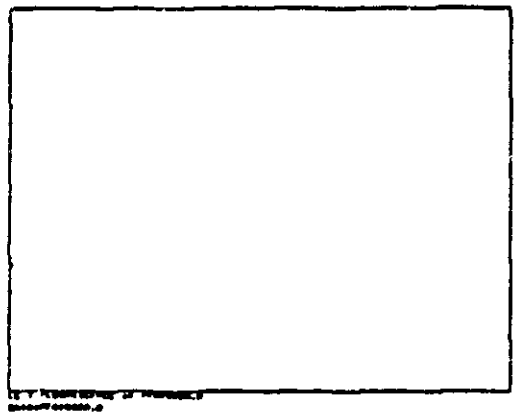


Figure 5-1. HPLC Chromatogram of standard solution

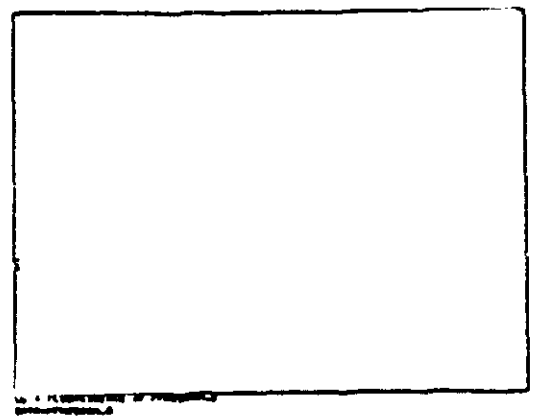


Figure 5-2. HPLC Chromatogram of blank blood plasma

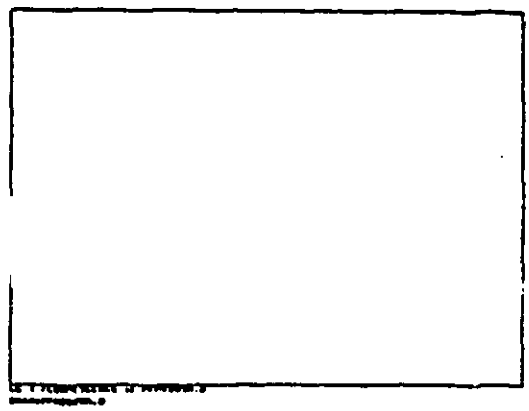


Figure 6. HPLC Chromatogram of patient's blood plasma (one hour after dosage)

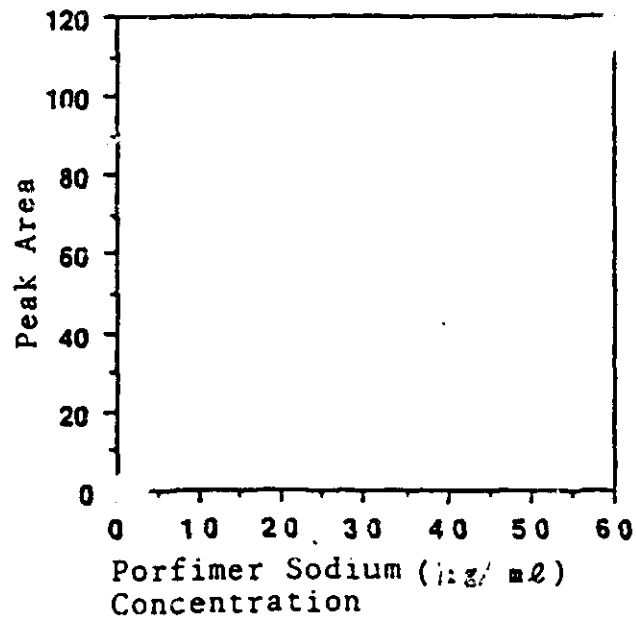


Figure 7. Derivation of graph line based on HPLC method

related substances, hematoporphyrin, hydroxyethylvinyl deuteroporphyrin and protoporphyrin were μg/ml, μg/ml and μg ml, respectively.

Typical HPLC chromatograms of a standard solution and blank blood plasma are shown in figure 5. It was discovered that the peak is maintained at the same time in the blank blood plasma as for the porfimer sodium and this peak derived from the gradient. A clear porfimer sodium peak was discovered in the HPLC chromatogram of the specimen (1.0 hour after dosage) but was hardly discovered at all for the related substances (figure 6).

(2) The concentrations of porfimer sodium in blood plasma of the four patients (mentioned above) measured by the HPLC method are shown in table 4. All of the related materials in the specimen were below the concentration detection limits. Virtually the same values were obtained for the each of the drawn blood scores for concentrations in the blood plasma for all four patients and they showed two compatible disappearance patterns.

Table 4. Concentration of Porfimer Sodium in Patients' Blood Plasma (HPLC Method)

Units: μg/ml

After Dosage (hours)	Subject (initials)				Average
Predose	ND	ND	ND	ND	
1					
3					
9					
24					
48					
72					
120					
168					
$\alpha T_{1/2}$(hr)					7.7
$\beta T_{1/2}$(hr)					250.2
AUC					974.3

ND Less than concentration detection limit (μg/ml)
- No specimen

STUDY NO: D73-P703

TABLE 1 SUMMARY OF PARTICIPATING COUNTRIES, CENTRES AND INVESTIGATORS

Patient Number	Batch Number	Treatment Date	Country	Trial Number	Investigator/Treatment Centre
	B90-0020	16.07.91	Spain	5	Dr Jose Pablo DIAZ JIMENEZ Clinica Tres Torres Doctor Roux 76 08017 Barcelona, Spain
	B90-0020 B90-0020 B90-0020	17.07.91 03.07.91 19.11.91	UK UK UK	6 6 6	Mr K MOGHISSI Consultant Cardiothoracic Surgeon Castle Hill Hospital Cottingham, Hull N Humberside HU16 5JQ, UK
	(Not (Available)	18.06.91 05.11.91 12.11.91	France France France	8 8 8	Dr Michel LEROY Service de Chirugie Thorocique Centre Medico-Chirugical FOCH 40 Rue Worth 92151 Suresnes Cedex, France
	B90-0186	26.06.91	Italy	9	Prof Pasquale SPINELLI Endoscopy Department Instituto Nazionale Tumori Via Venezian 1 Milan 20133 Italy
	B90-0020 B90-0020 B90-0020	29.07.91 29.07.91 04.11.91	Germany Germany Germany	10 10 10	Dr K HAUESSINGER Zentral Krankenhaus der LVA Oberbayern Unterbrunner Strasse 85 8035 Gauting Gauting bei Munchen Bayern, Germany
	B90-0020	09.09.91	Norway	16	Prof K Gierckosky Radiumhospitalet 0310 Montebello Oslo, Norway

* Non-randomised patients

50 34

Table 4 Summary of Patient Demographic Characteristics

Total Patients		12
Sex	Male	9
	Female	3
Age (years)	≤70	7
	>70	5
	Range	52 - 86
	Median	69
	Mean	69
Histology:	Carcinoma in-situ	1
	Epidermoid	1
	Large cell	1
	Pulmonal blastoma	1
	Squamous	7
	Undifferentiated	1
Karnofsky performance status (baseline)		
	50%	1
	60%	1
	70%	6
	80%	3
	90%	1
	100%	0

Please refer to Appendix VI-1 for demographic data and Appendix VI-2 for histological data and tumour location for individual patients.

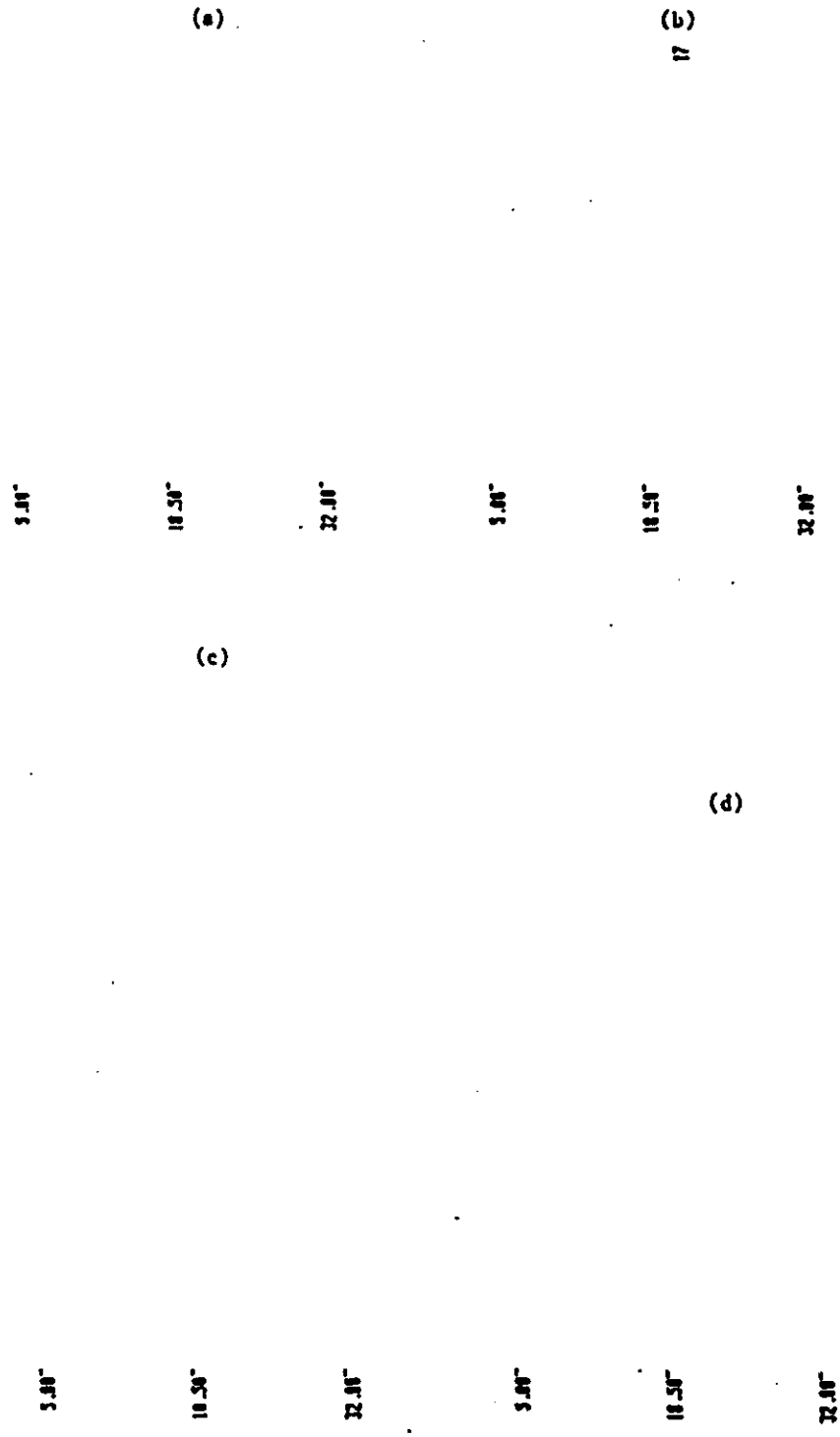
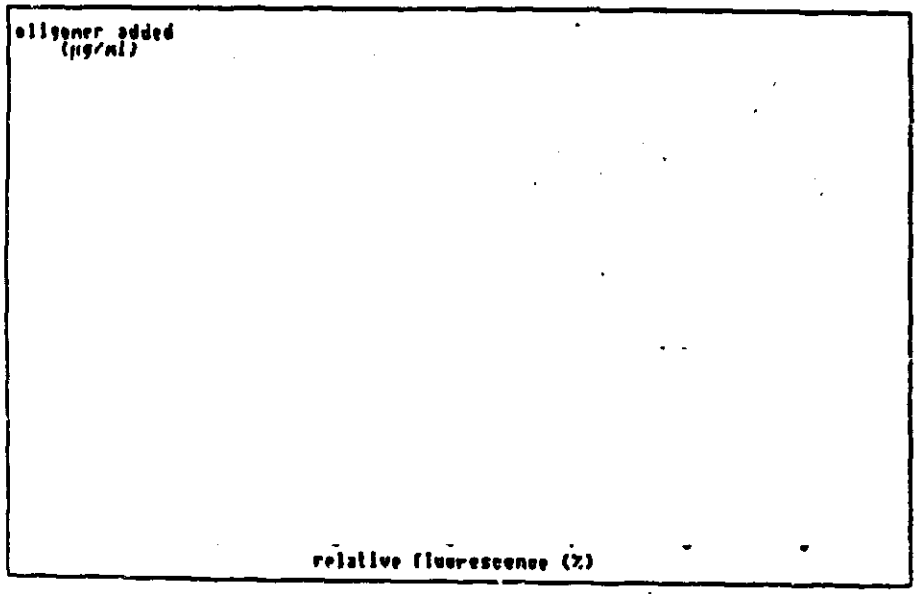


Figure 1. HPLC profile of drug extracted from blood of Patient (a) Photofrin as supplied (b)10 mins after administration (c) 1 hour after administration (d) 24 hours after administration. Subsequent samples showed no change in the profile. (Attenuations are different in the profiles shown).



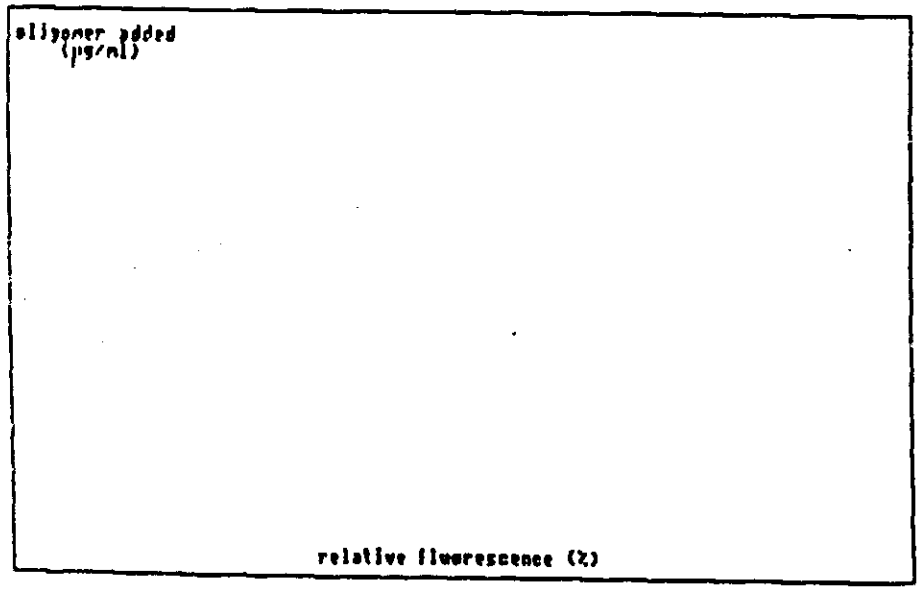


Figure 2. Calibration graphs for the determination of oligomer concentration from relative fluorescence. Those data in Table 8 marked with an asterisk were obtained from calibration graph (b). All other data were obtained from calibration graph (a).

Plasma Concentration vs. Time for 12 patients after a single I.v dose of photofrin (2 mg/kg)

Time	Plasma concentration (mcg/ml)		
	Patients		

Time	Mean	S.D	C.V (%)
	79.1	48.5	61
	53.2	16.0	30
	40.9	13.6	33
	32.9	11.6	35
	23.3	9.24	40
	14.9	5.93	40
	8.56	3.50	41
	5.58	2.55	46
	4.27	2.00	47
	3.41	1.56	46
	2.83	1.33	47
	2.01	1.15	57
	2.53	0.708	28
	1.44	0.635	44
	1.05	0.459	44
	0.819	0.366	45
	0.577	0.224	39
	0.439	0.162	37

NS – No Sample

Table 1

Pharmacokinetic Parameters for Photofrin II following a 2 mg/kg IV dose to Cancer Patients

SUBJECT	C_{max} (mcg/ml)	AUC_{0-T} (mcg.hr/ml)	AUC_{0-inf} (mcg.hr/ml)	CL_T (ml/hr/kg)	V_{ss} (L/kg)	$T_{1/2}$ (hr)
Mean	79.6	2460	2810	0.859	0.422	515
S.D	48.2	1029	1124	0.453	0.326	136
C.V (%)	61	42	40	53	77	26

*Patients died 27, 38 and 54 days, respectively, after dosing. None of the deaths were drug related.

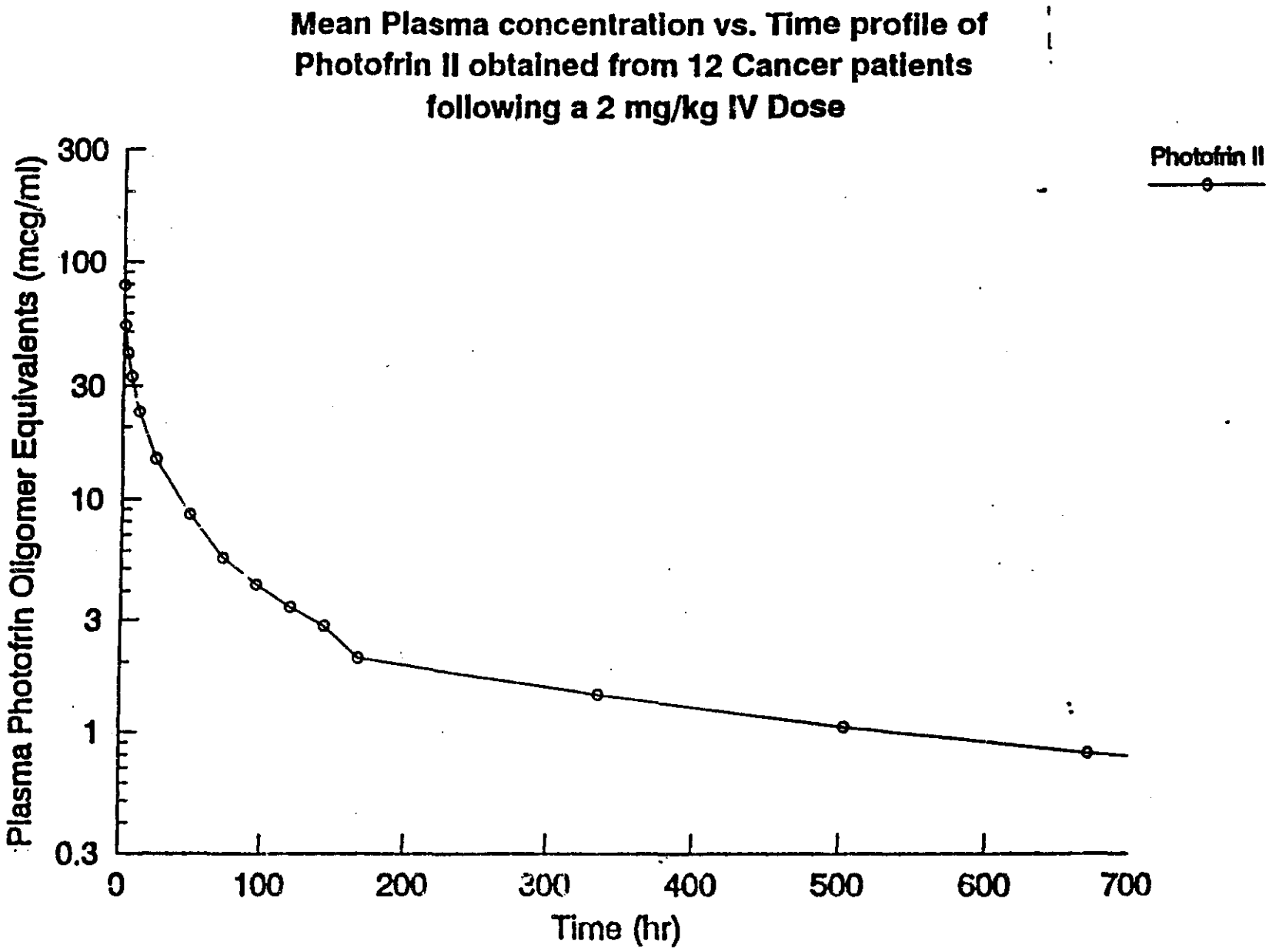

Mean Plasma concentration vs. Time profile of Photofrin II obtained from 12 Cancer patients following a 2 mg/kg IV Dose
Photofrin II
Plasma Photofrin Oligomer Equivalents (mcg/ml)
300
100
30
10
3
1
0.3
0
100
200
300
400
500
600
700
Time (hr)

Figure 1

REPORT NO: 2

Pharm/Tox

Memorandum — Department of Health and Human Services
Food and Drug Administration
Division of Oncology And Pulmonary Drug Products

Date: December 20, 1995

From: Joseph DeGeorge
Pharmacologist Team Leader, HFD 150

Subject: NDA 20,451 Photofrin
Failure of Sponsor to Respond Comments in Approvable Letter of July 13, 1995

To: File NDA 20,451

The Sponsor has not addressed questions 7 through 15, raised in the Approvable letter of July 13, 1995 in their resubmission. The concerns addressed in these questions were all related to the substitution of the in vitro/HPLC methodology and its validation as a substitute for the current in vivo method used to identify and assess Photofrin activity for release. As the Sponsor is at this time not seeking substitution of the in vivo methodology for the current approval, these questions are not germane to the approvability of NDA 20,451. The answers to these questions remain outstanding and will need to be addressed if substitution of the in vitro method is sought in future submissions.

cc:
Orig NDA
Div file
HFD/150 DMcGuinn
" JDeGeorge

Division of Oncology Drug Products
Review and Evaluation of Pharmacology and Toxicology Data
Comments on Labeling, Filename Fotolab3.nda
Review # 10

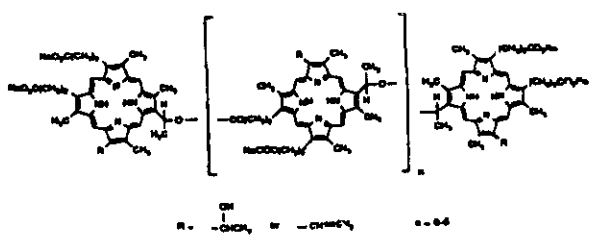
NDA 20-451 Reviewer: W. David McGuinn, Jr.,Ph. D.

Submission:	FAX submitted	October 13, 1995
	Completed	October 16, 1995
Official submission	AZ	December 6, 1995 — 2493 letter dated

Sponsor: QLT Phototherapeutics Inc.,
520 West 6th Avenue
Vancouver, British Columbia
Canada, V5Z 4H5

Information to be conveyed to the sponsor: YES

Drug Name: PHOTOFRIN® (Porfimer Sodium), or Photofrin II
Chemical Name: Dihematoporphyrin Esters
Structure



Indications: Esophageal Cancer

QLT has submitted a request to modify the labeling in the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection of the Precautions section. They have also requested to modify the Pregnancy section.

1) PHOTOFRIN is pregnancy class C. The Impairment of Fertility subsection of the Precautions section currently reads:

> PHOTOFRIN given to male and female rats intravenously, at 4 mg/kg/d (0.32 times the clinical dose on a mg/m^2 basis) before conception and through day 7 of pregnancy caused no impairment of fertility, but did cause hypertrophy of the ovaries and testes and decreased body weight in the parent rats.

The sponsor says that they disagree with the statement that PHOTOFRIN causes hypertrophy of the ovaries and testes. They state that "the increased weight of these organs was due to pigment accumulation, not an increase in the cell size (or cell number)." They ask that the section be changed to read:

PHOTOFRIN given to male and female rats intravenously, at 4 mg/kg/d (0.32 times the clinical dose on a mg/m^2 basis) before conception and through day 7 of pregnancy caused no impairment of fertility, but did cause decreased body weight in the parent rats.

The original company report is a "Reproductive Toxicity Study of 184,116 (PHOTOFRIN II; LHC 10,750) administered intravenously prior to and in the early stages of pregnancy in rats." #LJT1661R(E) Volume 22, page 191. In this study, rats were given 0, 0.5, 1.0, 2.0 and 4.0 mg/kg/d. Males were dosed for 63 days prior to mating and continuing until sacrifice. A subset of males was allowed to recover to day 118. Females were dosed for 14 days prior to mating and continuing until day 7 of pregnancy. The animals were necropsied, but tissues were not examined histologically. Body weight decreased with dose as did food consumption in animals receiving 2 and 4 mg/kg/d.

Absolute organ weight increased with dose in testes, kidney, spleen and probably liver. Lower liver weight seen in high dose males was probably due to liver damage. The relative organ weights of heart (119%), liver (133%), kidney (137%), spleen (305%), adrenal glands (150%), and testes (182%) increased with dose. The numbers shown in parenthesis by the organs are the percent of control in the high dose group. In the high dose group the testes of 10 of 10 rats were described as "pale brown".

The change in average weight for rat testes in the high dose group is from 3.20 ± 0.2 g (control) to 4.42 ± 0.92 g (high dose). If the sponsors hypothesis that the weight gain is due to "pigment accumulation" is correct, the testes of high dose rats would contain an average of 1.2 g of pigment. If this pigment was PHOTOFRIN, this much would certainly cause significant discoloration, more than "pale brown" as described in the report. More importantly, the accumulation of PHOTOFRIN to ⅓ the total weight of normal testes would be expected to be toxicologically significant. Also, a 300 g male rat given 4 mg/kg/d, or 1.2 mg, for 100 days would receive a cumulative dose of 120 mg. This total dose is one tenth the amount need to cause the observed weight change if this change is due to PHOTOFRIN accumulation. In this reproduction study, hypertrophy was described grossly in spleen of male and female rats. In other studies, once weekly exposure to 10 mg/kg of PHOTOFRIN for 13 weeks caused anorexia, weight loss and increased organ weights in ovaries and testes of rats. This exposure also caused increased weights in adrenals, thyroid and prostate in males and thymus in females. Sub-acute exposure caused changes in rat epididymis and seminal vesicles. These changes were not attributed to pigment accumulation. The sponsor provided no new data to support the hypothesis that the weight change is due to pigment accumulation. Hypertrophy, hyperplasia or edema are more plausible explanations for the increased weight in testes, nevertheless, it is not histologically confirmed in this reproduction study.

2) The original suggested labeling in the pregnancy section reads:

PHOTOFRIN given to rat dams during fetal organogenesis intravenously at 8 mg/kg/d (0.64 times the clinical dose on a mg/m^2 basis) caused no major malformations or developmental changes. This dose caused maternal and fetal toxicity resulting in increased resorptions, delayed ossification, decreased litter size, and reduced fetal weight. PHOTOFRIN caused no major malformations when given to rabbits intravenously during organogenesis at 8 mg/kg/d (1.5 times the clinical dose on a mg/m^2 basis).

PHOTOFRIN given to rats during late pregnancy through lactation intravenously at 4 mg/kg/d (0.32 times the clinical dose on a mg/m^2 basis), caused a reversible decrease in growth of offspring.

The sponsor proposes to modify the labeling to read (changes underlined):

> PHOTOFRIN given to rat dams during fetal organogenesis intravenously at 8 mg/kg/d (0.64 times the clinical dose on a mg/m^2 basis) for 10 days caused no major malformations or developmental changes. This dose caused maternal and fetal toxicity resulting in increased resorptions, delayed ossification, decreased litter size, and reduced fetal weight. PHOTOFRIN caused no major malformations when given to rabbits intravenously during organogenesis at 4 mg/kg/d (1.5 times the clinical dose on a mg/m^2 basis) for 13 days. This dose caused maternal toxicity resulting in increased resorptions, decreased litter size, and reduced fetal body weight..
>
> PHOTOFRIN given to rats during late pregnancy through lactation intravenously at 4 mg/kg/d (0.32 times the clinical dose on a mg/m^2 basis) for at least 42 days caused a reversible decrease in growth of offspring. Parturition and lactation were unaffected.

The sponsor has added or changed text for four reasons.

a) The highest dose in the rabbit study was 4 mg/kg/d not 8 mg/kg/d. This may have been my typographical error. The sponsor corrected the dose to 4 mg/kg/d, but did not change the ratio to the clinical dose. This should be changed to "0.65 times the clinical dose on a mg/m^2 basis."

b) The sponsor wants to add a brief description of the results of the rabbit segment II study. This is acceptable.

c) The sponsor wants to add the number of days animals were dosed "for completeness". This is acceptable though unnecessary.

d) The sponsor wishes to add the statement that "Parturition and lactation were unaffected" in the rat segment III study. Parturition was unaffected in by PHOTOFRIN. The study did not measure lactation except by observing nursing behavior, which was unaffected. The high dose caused a reversible decrease in growth of offspring. This suggests that PHOTOFRIN may have caused a change in lactation if not nursing behavior. The F_1 offspring of dosed dams were less nourished than those of control dams.

3) On page 42 of the official submission (a copy of the November 28, 1995 Fax, page 3) under Pharmacology, Toxicology, Biopharmaceuticals comment #1 the sponsor says that by law the trademark name cannot be used as an adjective as recommended in labeling comment 1 in the Approvable letter.

The label under CLINICAL PHARMACOLOGY currently reads:

"Intracellular PHOTOFRIN-PDT damage results from radical reaction."

This sentence may be changed to:

"Cellular damage caused by PHOTOFRIN-PDT is a consequence of the propagation of radical reactions."

Comments to sponsor:

1) The change in average weight for rat testes in the high dose group is from 3.20 ± 0.2 g (control) to 4.42 ± 0.92 g (high dose). If your hypothesis that the weight gain is due to "pigment accumulation" is correct, the testes of high dose rats would contain an average of 1.2 g of pigment. If this pigment was PHOTOFRIN, this much would certainly cause significant discoloration, more than "pale brown" as described in the report. Also, a 300 g male rat given 4 mg/kg/d, or 1.2 mg, for 100 days would receive a cumulative dose of 120 mg. This total dose is one tenth the amount need to cause the observed weight change if this change is due to PHOTOFRIN accumulation. In this reproduction study, hypertrophy was described grossly in spleen in male and female rats. In other studies, once weekly exposure to 10 mg/kg of PHOTOFRIN for 13 weeks caused anorexia, weight loss and increased organ weights in ovaries and testes of rats. This exposure also caused increased weights in adrenals, thyroid and prostate in males and thymus in females. Sub-acute exposure caused changes in rat epididymis and seminal vesicles. These changes were not attributed to pigment accumulation. You have provided no new data to support the hypothesis that the weight change is due to pigment accumulation, nor have you identified the brown pigment in the affected organs. Hypertrophy, hyperplasia or edema are more plausible explanations for the increased weight.

The section "Carcinogenesis, Mutagenesis, Impairment of Fertility" subsection on fertility, should be modified in accord with the following:

PHOTOFRIN given to male and female rats intravenously, at 4 mg/kg/d (0.32 times the clinical dose on a mg/m^2 basis) before conception and through day 7 of pregnancy caused no impairment of fertility. In this study, long term dosing with PHOTOFRIN caused discoloration of testes and ovaries and hypertrophy of the testes. PHOTOFRIN also caused decreased body weights in the parent rats.

2) Comments on your proposed changes in the Pregnancy section of the labeling.

a) Thank you for correcting the error describing the highest dose in the rabbit study. The ratio of this dose to the usual clinical dose should be changed to read "0.65 times the clinical dose on a mg/m^2 basis."

b) The addition of the results of the rabbit study is acceptable.

c) The addition of the number of days the animals were dosed is acceptable. Nevertheless, the duration of the studies are usually understood as standard.

d) The rat segment III study did not measure lactation except by observing nursing behavior, which was unaffected. The high dose cause a reversible decrease in growth of offspring. This suggests that PHOTOFRIN may have caused a change in lactation if not nursing behavior. The sentence "Parturition was unaffected." can be added.

3) To avoid using PHOTOFRIN-PDT as an adjective, the seventh sentence in the CLINICAL

PHARMACOLOGY section Pharmacology subsection may be change to read:

"Cellular damage caused by PHOTOFRIN-PDT is a consequence of the propagation of radical reactions."

12/12/95

W. David McGuinn, Jr., Ph.D.

Completed	October 16, 1995
Edited	December 6, 1995
Edited	December 11, 1995

cc:
Original NDA
HFD-150 Room File
HFD-150/W D McGuinn
HFD-150/J J DeGeorge
HFD-150/P Zimmerman

12/12/95
faxed 12/12/95 CFZ

Division of Oncology and Pulmonary Drug Products
Review and Evaluation of Pharmacology and Toxicology Data
NDA Supplement #1
Addendum to Review July 6, 1995

NDA 20-451
Serial BZ
Reviewer: W. David McGuinn, Jr.,Ph. D.

Submission:

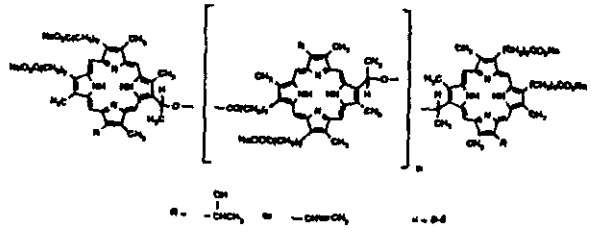
Supplement Dated	May 12, 1995
Received by CDER	May 16, 1994
Received by reviewer	May 18, 1994 Addendum Completed July 6, 1995

Sponsor:

QLT Phototherapeutics Inc.,
520 West 6th Avenue
Vancouver, British Columbia
Canada, V5Z 4H5

Information to be conveyed to the sponsor: NO

Drug Name: Photofrin® (Porfimer Sodium), or Photofrin II
Chemical Name: Dihematoporphyrin Esters
Structure



Indications: Esophageal Cancer

Dosage Forms and Route of Administration:

Photofrin® is administered *i.v.* in dextrose$_{(aq)}$ (5%) or 0.9% Sodium Chloride (USP) at a dose of 2.0 mg/kg. It is reconstituted from a lyophilized powder. Forty to 50 hr after dosing, 630 nm light from a laser is transmitted to the tumor site through an optical fiber light guide at a predetermined power and energy.

Summary from initial review

QLT has attempted to develop an HPLC assay to replace the mouse tumor-implant bioassay. QLT now uses this bioassay to assure the batch-to-batch safety and efficacy of PHOTOFRIN. In this new HPLC assay a large group of unresolved chromatographic peaks form an integrated area called Region 3. When PHOTOFRIN is irradiated in solution the %area of Region 3 decreases, PDT efficacy decreases proportionately. When lyophilized PHOTOFRIN is degraded by pyrolysis (to 80C for 14 days) the %area of Region 3 increases but PDT efficacy is unaffected. This suggests that pyrolysis of solid PHOTOFRIN and photolysis of PHOTOFRIN in solution involve two different chemical reactions. Both reactions change the %area of Region 3, but affect PDT activity

differently. The current HPLC assay cannot distinguish between these reactions. %area Region 3 does not consistently predict PHOTOFRIN PDT efficacy. Thus, as it is now designed, this assay is not adequate to replace the tumor implant bioassay. Nevertheless, these results are encouraging. They suggest that QLT can eventually develop an acceptable HPLC assay to replace the bioassay.

Recommendation

The development of an analytical assay to replace the currently used mouse tumor-implant bioassay is not required for approval of this NDA.

W. David McGuinn, Jr., Ph. D.

July 6, 1995

cc:
Orig NDA
DIV file
HFD-150/Zeminn
" /D. McGuinn
" /L DeGeorge
" /R Justice

July 6, 1995

7/6/95

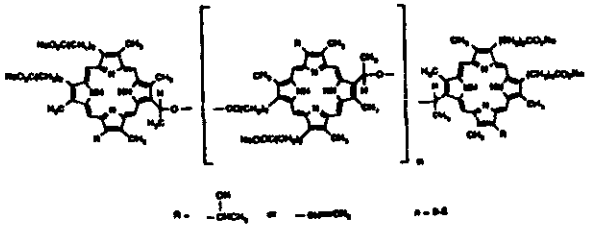
Division of Oncology and Pulmonary Drug Products
Review and Evaluation of Pharmacology and Toxicology Data
NDA Supplement #1

NDA 20-451 Reviewer: W. David McGuinn, Jr.,Ph. D.
Serial BZ
Submission: Suppliment Dated May 12, 1995
Received by CDER May 16, 1994
Received by reviewer May 18, 1994 Completed June 29, 1995

Sponsor: QLT Phototherapeutics Inc.,
520 West 6th Avenue
Vancouver British Columbia
Canada, V5Z 4H5

Information to be conveyed to the sponsor: YES

Drug Name: Photofrin® (Porfimer Sodium), or Photofrin II
Chemical Name: Dihematoporphyrin Esters
Structure



Indications: Esophageal Cancer

Partial list of Related IND's and NDA's

IND

IND

The FDA granted Photofrin orphan drug designation June 6,1989 for use against esophageal carcinoma. On April 22, 1991, the FDA granted Photofrin designation as a drug intended to treat life-threatening and severely debilitation diseases under 21 CFR 321 Sub-part E for esophageal cancer.

Dosage Forms and Route of Administration:

Photofrin® is administered *i.v.* in dextrose$_{(aq)}$ (5%) or 0.9% Sodium Chloride (USP) at a dose of 2.0 mg/kg. It is reconstituted from a lyophilized powder. Forty to 50 hr after dosing, 630 nm light from a laser is transmitted to the tumor site through an optical fiber light guide at a predetermined power and energy.

Studies Reviewed

1) Development of a Bioactivity Indicating Reverse Phase HPLC Method for Assay of PHOTOFRIN Porfimer Sodium. QLT Phototherapeutics Inc., May 1, 1995.

Appendices (reviewed)

1) Development of a Bioactivity Indicating HPLC Method for PHOTOFRIN.
2) Validation of the HPLC Method as an Alternative to the Bioassay for PHOTOFRIN.
3) Qualification of the BIHPLC Method as an Assay of PHOTOFRIN.
4) Validation of the BIHPLC Method for PHOTOFRIN Analysis.

Studies not reviewed (Journal Articles submitted as references).

1) R. L. Lipson, E. J. Baldes and M. J. Gray, 1967, Hematoporphyrin Derivative for detection and Management of Cancer, *Cancer*, **20**:2255-2257.
2) T. J. Dougherty, G. B. Grindey, R. Fiel, K. R. Weishaupt and D. G. Boyle, 1975, *J. Nat. Cancer Instit.*, **55**(1):115-119.
3) T. J. Dougherty, 1983, Hematoporphyrin as a photosensitizer of tumors. *Photochemistry and Photobiology*, **38**(3):377-379.
4) Y. K. Ho, J. R. Missert and T. J. Dougherty, 1991, Activity and Physiocochemical properties of PHOTOFRIN, *Photochemistry and Photobiology*, **54**(1):83-87.
5) R. K. Pandey, K. M. Smith, and T. J. Dougherty, 1990, Porphyrin Dimers as Photosensitizers in Photodynamic Therapy, *J. Medicinal Chemistry*, 33(1):2032-2038.

Summary

QLT has attempted to develop an HPLC assay to replace the mouse tumor-implant bioassay. QLT now uses this bioassay to assure the batch-to-batch safety and efficacy of PHOTOFRIN. In this new HPLC assay a large group of unresolved chromatographic peaks form an integrated area called Region 3. When PHOTOFRIN is irradiated in solution the %area of Region 3 decreases, PDT efficacy decreases proportionately. When lyophilized PHOTOFRIN is degraded by pyrolysis (to 80C for 14 days) the %area of Region 3 increases but PDT efficacy is unaffected. This suggests that pyrolysis of solid PHOTOFRIN and photolysis of PHOTOFRIN in solution involve two different chemical reactions. Both reactions change the %area of Region 3, but affect PDT activity differently. The current HPLC assay cannot distinguish between these reactions. %area Region 3 does not consistently predict PHOTOFRIN PDT efficacy. Thus, as it is now designed, this assay is not adequate to replace the tumor implant bioassay. Nevertheless, these results are encouraging. They suggest that QLT can evenutally develop an acceptable HPLC assay to replace the bioassay.

Recommendation

The HPLC assay as described in this submission is not adequate to replace the mouse bioassay currently used to assure the efficacy of PHOTOFRIN batches.

Comments to the Sponsor

1) Why are two peaks in the PHOTOFRIN chromatogram on page 10 and elsewhere marked Hydroxyethylvinyldeuteroporphyrin (HVD)? Are two similar peaks eluted with this system when HVD standards are chromatographed?
2) The scale of the chromatograms in the submission varies. Was the PHOTOFRIN sample concentration standardized for the HPLC separations?
3) Were the batches used to define and validate the BIHPLC assay manufactured under scheme

4) You could have prepared the Region 3 reduced sample (appendix 2, page 97) by HPLC purification of PHOTOFRIN similar to the preparation of the Region 3 enriched sample. Hp and HVD together do not appear to account for most of the area in R2. The contribution of the other peaks in PHOTOFRIN chromatographic regions R1 and R2 cannot be determined. The analysis assumes there is no efficacy threshold for some other component of R1 or R2 (non-linear dose response) and that Hp and HVD are completely ineffective. The latter of these two assumptions is not well supported, since this sample had an unexpectedly low ED_{50} (4.7 mg/kg). If no PHOTOFRIN activity is associated with Region 2, the intercept of the linear analysis should be statistically equal to 0. Yet, this intercept value is .21 (close to the $1/ED_{50}$ value of the Region 3 reduced sample).
5) The two points from the Region 3 manipulated samples have an inappropriately large influence on your linear analysis. They are far outside the range of the other points and are un-weighted. Also the point at ED_{50} = 1.02 X %area =34.4 in the photolysis experiment appears an outlier only when the data are analyzed using the reciprocal of ED_{50}. When ED_{50} is plotted directly against %area, this point is an important part of the dose response. Please explain why this point was excluded.
6) If the change in $1/ED_{50}$ from these PHOTOFRIN samples results from the variation of a single linear parameter, the slopes derived from the three experiments should be statistically indistinguishable. The individual slopes are 0.03 (photolysis), 0.0006 (pyrolysis) and 0.009 (R3-manipulated). The Student's-t statistic for the slopes from the photolysis and pyrolysis data is significantly larger than the tabular t value indicating that the slopes are significantly different. These lines are not parallel. The slopes and intercepts for all three lines appear from the graph to be different. Please explain why these experiments were combined for this analysis?

   A linear analysis can sometimes be used to describe a dose response within the pseudo-linear region of the curve when the curve is well defined. Nevertheless, the photolysis experiments do not vary %area R3 across a sufficiently wide range to adequately define the upper and lower limits of a dose response curve. The pyrolysis experiments demonstrate no dose response and the manipulated R3 samples are probably not measuring the same pseudo-linear phenomenon. The relationship between ED_{50} and %area R3 will probably be better analyzed as a reverse-sigmoidal dose response where integrated %area is the dose and ED_{50} is the response. A replot of the raw data from the pyrolysis experiment suggests such a relationship. You should use such a dose response analysis to specify acceptable limits for the %area from lower (ED_{50} = x mg/kg) and upper (ED_{50} = y mg/kg) dose response values.
7) Since a dose response relationship probably exists between some component of Region 3, what is the rational for using three standard deviations from the batch-to-batch mean %area Region 3 to define the limits for batch acceptability? How do these limits relate to the dose response? Batches P91-164 and P91-163 had %area Region 3 values of 32.3 and 31.1 respectively in the experiments used to calculate this batch-to-batch mean (Appendix 1, page 81). These batches had %area Region 3 values of 35 and 36 respectively in subsequent experiments to determine the dose response

(Appendix 2, page 102). What caused this difference? Using the limits defined from the batch-to-batch mean and standard deviation of Appendix 1, samples with only 2% higher %area Region 3 values than these obtained for P91-164 and P91-163 in Appendix 2 would be rejected.

8) In future submissions please include the raw data from the ED_{50} experiments. How many points did you use to determine ED_{50}? How many animals were in each dose group?

9) The results these PHOTOFRIN degradation studies (photolysis and pyrolysis) imply that Region 3 of the chromatogram contains at least two components that significantly affect the integrated %area. The concentration of one component increases with pyrolysis of the lyophilized powder yet does not influence PDT efficacy. That of another decreases with photolysis of reconstituted PHOTOFRIN and is central to the mechanism of PDT. The current HPLC assay cannot distinguish between these two components and thus cannot predict batch-to-batch efficacy or uniformity. For example, a batch exposed to excess heat might be rejected because the %area of Region 3 was to great, yet the batch would pass the bioassay.

This finding is not discouraging. It suggests that better chromatographic separation or defining smaller chromatographic regions may distinguish the component within R3 that correlates with activity. This method cannot as yet replace the bioassay used to assure the efficacy of each batch of PHOTOFRIN, but such a replacement is probably attainable.

W. David McGuinn, Jr., Ph. D.

Completed June 29, 1995
Final modification July 7, 1995

July 7, 95

Review

QLT has as yet been unable to isolate the chemical compounds within PHOTOFRIN that generate oxygen radicals when irradiated. These radicals cause the cell damage necessary for effective Photodynamic Therapy (PDT). Thus, QLT cannot chemically characterize synthetic PHOTOFRIN to assure batch to batch therapeutic consistency. To assure therapeutic potency, QLT developed a bioassay. Briefly, mice are implanted with subcutaneous tumors. When the tumors are palpable, investigators inject the mice i.p. with a standard dose of PHOTOFRIN. The next day the tumors are irradiated through the skin with a standard dose of white light from a xenon-arc lamp. Mice with no sign of tumor after seven days are considered responders. Mice with any tumor are non-responders. A batch is accepted as good if $3 \leq$ # of responders ≤ 9. See my review of this assay June 27, 1995 and the original submission (protocol TX-3001(2), volume 5B, original NDA submission, p 176) for more information.

This bioassay is difficult, expensive and time consuming. It is unusually sensitive to investigator

technique. The results could easily drift over time. Nevertheless, within its many limits the assay does adequately define batch potency as a function of response. The assay can distinguish between subpotent, potent and superpotent batches with some statistical confidence.

To circumvent the difficulties of this bioassay, QLT has attempted to develop an HPLC assay to replace it. They separated samples of PHOTOFRIN with the following system:

Waters 600E HPLC system
Waters 991 Photo-diode array detector set at 405 and 410 nm
Beckman Ultrasphere ODS 5 µm, 4.6 mm X 25 cm column
flow 1.6 ml/min, 25 min run time, 20 µl injection volume
solvents Ammonium Sulfate$_{(aq)}$(0.0066 g/ml)/acetonitrile/acetic acid, 3:7:1 v/v
Ammonium Sulfate$_{(aq)}$(0.0066 g/ml)/tetrahydrofuran/acetic acid, 3:7:1 v/v
complex gradient.

The following chromatogram is an example of this separation.

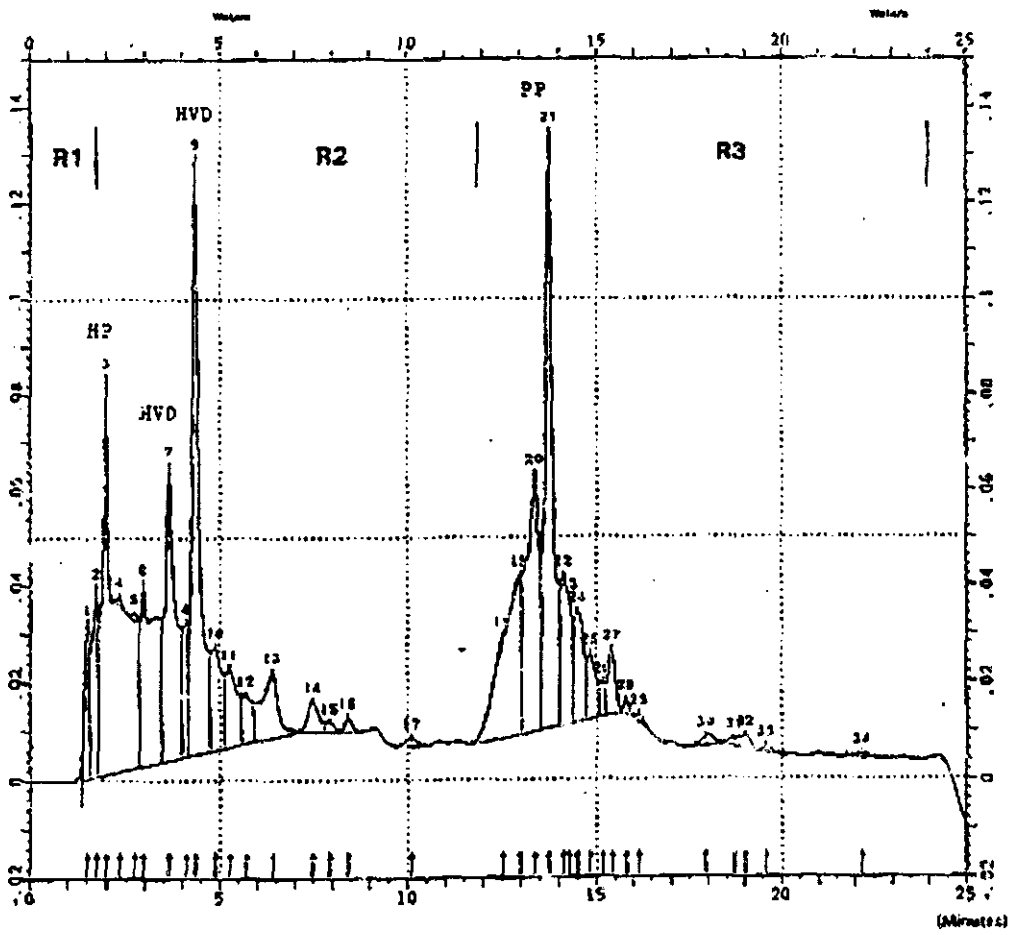


FIGURE 1. A chromatogram of a PHOTOFRIN® sample which passed the bioassay.

QLT arbitrarily divided the chromatograms into three regions. Region 1 is roughly the first two minutes of the run. Region 2 is from two minutes to the lowest valley between 10 and 11.5 minutes. It includes the first major complex of peaks and the Hematoporphyrin (Hp) peak. Region 3 is the rest of the chromatogram to 22 minutes and includes the second main complex of unresolved peaks. The following porphyrin monomers are prominent on the chromatogram.

Hematoporphyrin ~2 minutes
Hydroxyethylvinyldeuteroporphyrin (HVD) ~3.5 minutes and ~4.3 minutes
Protoporphyrin (Pp) ~14.5 minutes

The sponsor does not explain why two peaks are marked HVD.

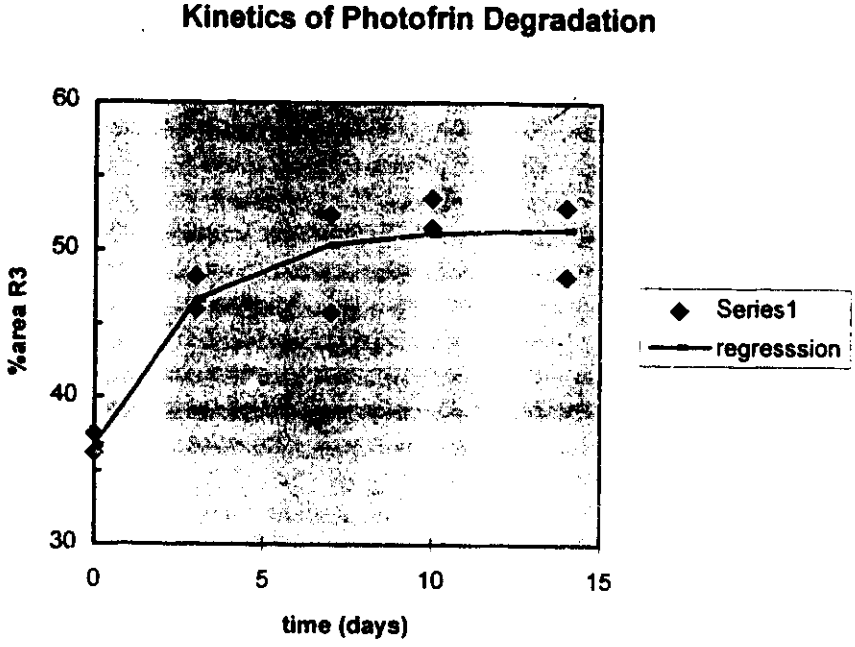
Appendix 1 of this supplement describes the initial development of the assay, but with little greater detail than the summary. It shows that the integrated peak areas of R1 and R3 of biologically active samples are different from the areas of inactive samples by Student's t-test. QLT used the results from the HPLC analysis of retention samples of seven clinical batches manufactured between March 1990 and December 1991 to establish the mean and standard deviation of the three regions. They propose to use these means ± 3 standard deviations as the limits for accepting a manufactured batch. QLT does not specify acceptable limits for Region 2 since changes in the area of this region do not correlate with biological activity.

R1 = 5.1 ± 3 %area proposed limits 2.1 to 8.1
R2 = 64.6 ± 1.7 %area
R3 = 30.2 ± 2.3 %area proposed limit 23.3 to 37.1

Notice that the sponsor did not determine these proposed limits as a function of biologic activity. Instead they set the limits at large and arbitrary deviations from the mean %areas of previously manufactured batches. I cannot determine from the text or previous submissions under which synthetic scheme (I, IR or II) these batches were manufactured.

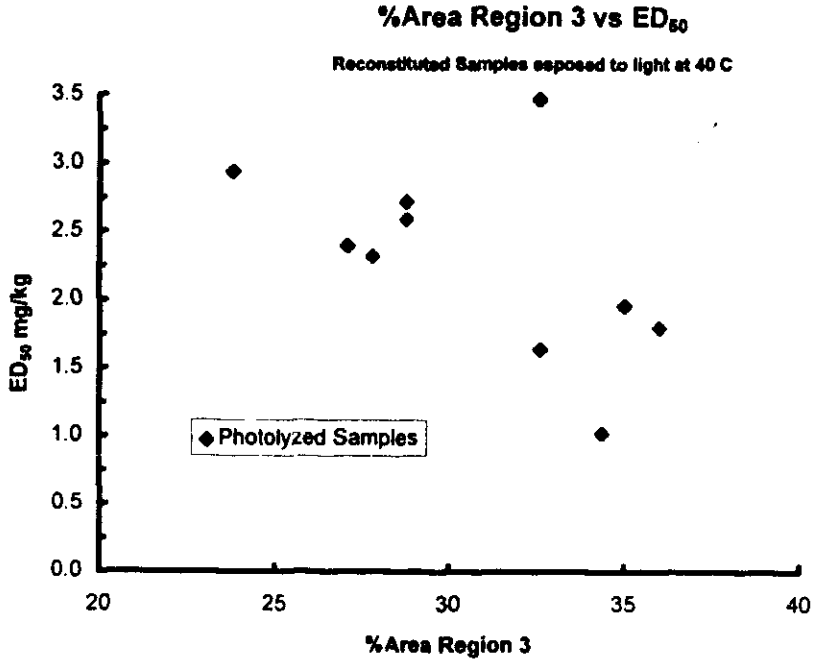
In these initial experiments, QLT also determined that lyophilized samples exposed to white or room light and elevated temperatures (65 or 85C) for 5 or 10 days retained biological activity. %area R3 increased in these samples with increased time and temperature, R2 decreased proportionately. R1 remained small and relatively constant. When reconstituted samples (in saline or dextrose solution) were exposed to incandescent light, biological activity decreased with %area R3. The biological activity and %area R3 of these reconstituted samples also decreased when the samples were stored at elevated temperatures (40 or 55C) for 5 or 10 days. Long term storage (24 months) at -20C affected neither biological activity nor %area R3. In these experiments, %area R1 usually changes inversely with %area R3. R2 changes little.

In appendix 2 the sponsor attempts to establish a linear correlation between %area Region 3 and ED_{50}. They laboriously determined the ED_{50} using the mouse assay described above. QLT does not specify the number of mice per dose data point or the number of data points. They used a log-probit model to determine ED_{50}. The investigators varied the %area of R3 by degrading PHOTOFRIN samples from two production batches with light and heat. The %area of R3 increased toward an exponential asymptote of about 50% when dry lyophilized samples were kept at 80C for 14 days in the dark. The following graph shows this increase.



This increase in %area R3 does not result in a decrease in ED_{50} (linear correlation coefficient 0.01). Under these conditions %area R2 decreases as %area R3 increases. %area R1 remains constant.

When samples from these same lots were reconstituted in solution and exposed to incandescent light at 40C for up to 40 hours, %area R3 decreased almost linearly with time to a values of less than 25%. This was not a minimum and longer irradiation would probably show a distinct exponential decay. QLT used an exponential model to describe this decay. In this experiment, ED_{50} increased from less than 2 to more than 3 mg/kg as %area R3 decreased from more than 35 to less than 25%. The following graph shows this increase in ED_{50}.

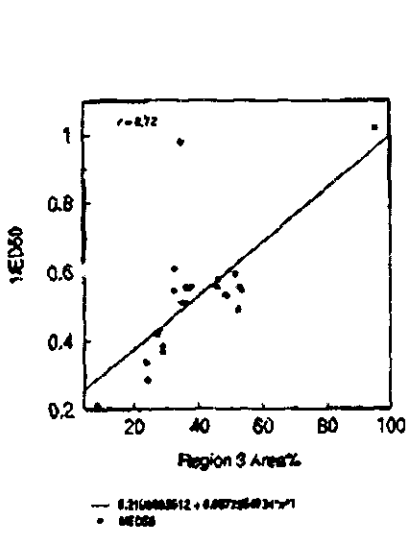


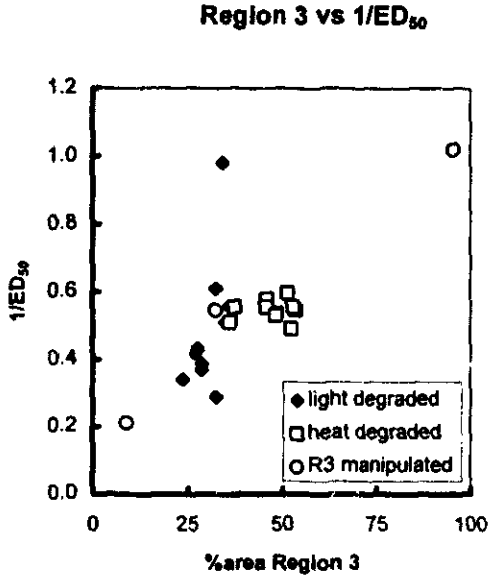
The linear correlation between these parameters is poor (correlation coefficient 0.31), but this is expected since this relationship is a dose response. A reverse sigmoid would probably fit this data better than a line. A true sigmoidal relationship cannot be confirmed since %area R3 changes over a relatively narrow range and the maxima and minima for ED_{50} are not confirmed. The large variation in this relationship is probably associated more with the bioassay or with the variable composition of R3 than with the HPLC determination of %area R3. Under these conditions %area R2 remained constant and %area R1 increased as %area R3 decreased.

The sponsor related %area R3 to ED_{50} in three other samples: another control, an R3 reduced sample, and an R3 enriched sample. The R3 reduced sample was prepared by adding Hp and HVD to PHOTOFRIN in a ratio of 5:1:1 w/w. This sample provides little useful information since the ED_{50} is more a measure of the efficacy of pure Hp than a measure of the efficacy of PHOTOFRIN fraction R2. Hp and HVD together do not account for the majority of the area in R2. The contribution of the other peaks in PHOTOFRIN chromatographic regions R1 and R2 cannot be determined. The analysis assumes that there is no efficacy threshold for some other component of R1 or R2 (non-linear dose response) and that Hp and HVD are completely ineffective. The latter of these two assumptions may be a particularly bad, since this sample had an unexpectedly low ED_{50} (see below).

The R3 enhanced sample was prepared by purifying R3 chromatographically and adding this partially purified fraction back to a PHOTOFRIN sample. This method reasonably simulates a sample with excess R3 if we assume that the chromatographic process does not modify PHOTOFRIN. This is not necessarily a good assumption, since PHOTOFRIN contains complex aggregates. R2 and R1 could have been similarly isolated and added to photofrin samples to decrease the relative area of R3. This possibly would have been a more useful method for preparing the R3-reduced sample and for the whole experiment. Data points generated by chromatographic partial purification over the entire range of values for %area R3 might have provided better information about the dose response than samples generated by pyrolysis and photolysis.

The sponsor combines the data from the heat degraded, light degraded and R3 manipulated experiments to determine the relationship between %area R3 and ED_{50}. QLT presented the following figure on the left to support this analysis. I replotted the data in the figure on the right to show the points from the different experiments with different symbols.





The sponsor then determined a linear correlation for the entire data set from the three experiments. In this analysis they excluded the point (1.04 $1/ED_{50}$ X 34.4 %area R3) because it was an "obvious outlier." When ED_{50} is plotted directly against %area this point is an important part of the dose response, thus there is no reason to exclude this point from the analysis. With this point excluded, the sponsor calculated a linear relationship with a correlation coefficient of 0.90, when it is included the value is 0.72.

The points from the R3-enriched and R3-reduced samples have a large influence on this linear analysis. These points were not weighted and their toxicological relevance is questionable, particularly since they were prepared by different method from each other and from the other two experiments. The R3 reduced data point presents the greater problem for the linear analysis. QLT asserts that efficacy is related only to %area R3 and that %area R2 does not contribute. Yet, the linear analysis predicts an intercept of ~ 0.2 (ED_{50} ~ 5 mg/kg at %area R3 = 0). This implies significant efficacy associated with R2 or with the compounds used to spike the R3-reduced sample, Hp and HVD. This problem probably does not result from true activity in R2 but from the artificiality of the linear analysis and the preparation of the R3-reduced sample.

I do not understand why QLT included the pyrolysis data in the linear analysis. They had stated that changes in %area R3 associated with heating time did not change the efficacy of these samples. The data points form a cluster (squares in graph on the right) that increases the correlation coefficient of the analysis, but the increase is irrelevant. If the change in ED_{50} from these PHOTOFRIN samples results from the variation of a single linear parameter, the slopes derived from the three experiments should be statistically indistinguishable. The individual slopes are 0.03 (photolysis), 0.0006 (pyrolysis) and 0.009 (R3-manipulated). I calculated the Student's-t statistic for the slopes from the photolysis and pyrolysis data. This statistic is significantly larger than the tabular t value indicating that the slopes are significantly different. These lines are not parallel. The slopes and intercepts for all three lines appear

from the graph to be quite different. Despite the large variation in the data it is unlikely that any other statistical comparisons would indicate equivalence. A linear analysis can sometimes be used to describe a dose response within the pseudo-linear region of the curve when the curve is well defined. Nevertheless, the photolysis experiments do not vary %area R3 across a sufficiently wide range to adequately define the upper and lower limits of a dose response curve. The pyrolysis experiments demonstrate no dose response and the manipulated R3 samples are probably not measuring the same pseudo-linear phenomenon. The relationship between ED_{50} and %area R3 will probably be better analyzed by a reverse-sigmoidal dose response than by a line.

This attempt to correlate %area R3 with biological activity points out a more serious problem with the BIHPLC assay. When lyophilized samples are heated, %area R3 increases but biological activity remains constant. When reconstituted samples are irradiated, %area R3 decreases and so does biological activity. These results imply that R3 contains at least two components that significantly affect the %area. One chemical component increases with dry pyrolysis yet does not influence activity. Another decreases with solution photolysis and is central to the mechanism of PDT. The current HPLC assay cannot distinguish between these two components and thus cannot predict batch to batch efficacy or uniformity.

Appendix 3 is a batch-to-batch qualification of the BIHPLC assay. It dose indicate that %area R3 and PDT efficacy are consistent among batches. Appendix 4 is an attempted validation of the BIHPLC assay. This section defines the accuracy, precision, ruggedness and linearity of the HPLC method. The method accuracy was between 96.4 and 99.8%. The method precision for R3 was 1.52% (repeatability).

The finding of these studies are not discouraging. They suggest that a better chromatographic separation or defining smaller regions may distinguish these components within R3. Such a separation might define a compound or at least a smaller chromatographic region that correlates directly with activity. This method cannot as yet replace the bioassay used to assure the efficacy of each batch of PHOTOFRIN, but such a replacement may be attainable.

cc:
Original NDA
HFD-150
HFD-150/W D McGuinn
HFD-150/J J DeGeorge
HFD-150/P Zimmerman
HFD-150/G Williams
HFD-150/Y Hsieh

Division of Oncology and Pulmonary Drug Products
Review and Evaluation of Pharmacology and Toxicology Data
Original Summary, Filename Fotofrin.nda

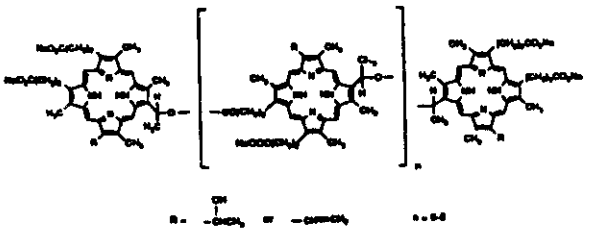
NDA 20-451 Reviewer: W. David McGuinn, Jr.,Ph. D.

Submission:
IND Dated April 12, 1994
Received by CDER April 13, 1994
Received by reviewer April 15, 1994 Completed August 12, 1994
Revised September 16, 1994

Sponsor:
QLT Phototherapeutics Inc.,
520 West 6th Avenue
Vancouver, British Columbia
Canada, V5Z 4H5

Information to be conveyed to the sponsor: YES

Drug Name: Photofrin® (Porfimer Sodium), or Photofrin II
Chemical Name: Dihematoporphyrin Esters
Structure



Indications: Esophageal Cancer

Partial list of Related IND's and NDA's

IND

IND

IND

Also see DMF

The FDA granted Photofrin orphan drug designation June 6,1989 for use against esophageal carcinoma. On April 22, 1991, the FDA granted Photofrin designation as a drug intended to treat life-threatening and severely debilitation diseases under 21 CFR 321 Sub-part E for esophageal cancer.

Dosage Forms and Route of Administration:

Photofrin® is administered *i.v.* in dextrose$_{(aq)}$ (5%) or 0.9% Sodium Chloride (USP) at a dose of 2.0 mg/kg. It is reconstituted from a lyophilized powder. Forty to 50 hr after dosing, 630 nm light from a laser is transmitted to the tumor site through an optical fiber light guide at a predetermined power and energy.

Patient Population:

The sponsor proposes Photofrin be labeled for use in Photodynamic Therapy for the reduction of obstruction and palliation of dysphagia in patients with completely or partially obstructing esophageal cancer.

Warnings:

Patients with porphyria or with known allergies to porphyrins should not receive Photofrin. Photodynamic therapy is contraindicated in patients with existing tracheoesophageal or bronchi-esophageal fistula. Photofrin causes profound photosensitivity. Physicians must caution patients to avoid bright light, sunlight or fluorescent light for 4 to 6 weeks. Patients have suffered severe sunburns after taking Photofrin. Bright light can cause irreversible retinal damage. Patients should ware sun-glasses that transmit less than 95% ambient light for at least 30 days. The patient should ware protective clothing for at least 30 days. Nevertheless, the patient should not remain in complete darkness, because light eliminates Photofrin from the skin by photo-bleaching. The label lists Photofrin as pregnancy class C. Photofrin in the absence of light has shown no significant genotoxicity or mutagenicity.

Introduction:

Photofrin is a mixture of dihematoporphyrin aggregates and oligomers linked by esters and ether bonds. Tumor cells and some normal tissues selectively retain these porphyrin oligomers by as yet ill defined mechanisms. Photofrin has little significant systemic biological activity and the clinical dose is only mildly toxic. Nevertheless, intracellular Photofrin is profoundly cytotoxic when irradiated with visible light (<630 nm). Most investigators agree that this cytotoxicity results from the production of singlet oxygen by energy transfer from the Photofrin first excited state. Singlet oxygen then initiates radical chain reactions that destroy cell membranes. This process is known as photo-dynamic therapy (PDT). PDT kills tumor cells *in vitro* and tumors *in vivo*. Photofrin is also used for the fluoroscopic detection of neoplastic lesions (D. G. von-Reuden *et al. J. Surg. Oncol.*, May 1993, 53(1) 43-46).

Manyak *et al.* have reviewed the use of PDT in the treatment of cancer (*J. Clin. Oncol.*, Feb. 1988, 6(2):380-391). PDT has been used to treat lung cancer (*e.g.* E. S. Edell and D. A. Cortese, *Mayo Clin. Proc.*, 1987, 62:8-14), recurrent laryngeal papillomas (*e.g.* A. L. Abramson *et al., Arch. Otolaryngol. Head Neck Surg.*, Jan. 1992, 118:25-29) bladder cancer (*e.g.* B. P. Shumaker and F.W. Hetzel, *Photochem. Photobiol.*, 1987, 46:899-901) esophageal cancer (*e.g.* V.G. Schweitzer *et al., Laryngoscope*, 1993, 103:699-703) and others tumors. Over 360 published studies describe the mechanism, pharmacology, efficacy and relative safety of this therapy.

In this review, HPD refers to the original hematoporphyrin derivative. In the original HPD, the ratio of ester links to ether links between porphyrin molecules forming the oligomers is high. Photofrin refers to a mixture of porphyrin oligomers and aggregates partially pruified from HPD. Much of the

literature refers to Photofrin as Photofrin II. Photofrin is isolated as the first fraction of HPD eluted from gel filtration columns, i.e. largest molecular weight components. This filtration eleminates much of the unreacted starting material, hematoporphyrin, and other porphyrin monomers. The chemist's review referres to this partially purified initial formulation as Photofrin IR. All the original, comprehensive GLP pre-clinical single and multiple dose studies were done with HPD or Photofrin IR. I found no pre-clinical studies that I could confirm the researchers studied the Photofrin now used clinically.

This newer Photofrin formulation, used clinically since about 1991, is reacted longer at high temperature than the original HPD. Longer reaction time decreases the ratio of ester to ether links between porphyrin monomers. The mixture is then partially purified by the same gel filtration method as the original Photofrin (IR). The sponsor believes the compounds created by this revised synthesis are the same as in the original mixture, only the ratio of ester to ether links is changed. The sponsor has not accurately determined these ratios. See the chemistry review for more details. There is no significant pre-clinical data describing the histopathology or toxicity of the Photofrin QLT is now supplying for clinical studies.

Studies Previously Reviewed:

The numbers in parentheses are the reference numbers in the non-clinical Pharmacology and Toxicology section of the NDA. I have identified Lot numbers where ever possible to show which Photofrin formulation the researchers used in a particular study. Copies of all but the first of these reviews are appended.

I) The following studies were reviewed by Dr. A.W. Coulter, October 1984. An older formulation of HPD was used in these studies. Subsequent studies supersede these so a copy is not included.

1) Acute toxicity studies in mice and dogs.
2) Pharmacology study in mice.
3) Pharmacokinetic studies in mice, monkeys and humans.

(II) The following studies were reviewed by Dr. A.S. Taylor, Jan. 21. 1989.

1) Pharmacological evaluation. (#118, 119, lots 223, 224, 225).
2) Acute toxicity in mice (# 125, lot 86048).
3) Phototoxicity study in mice. (# 126, lot 86048).
4) Acute toxicity in rats (#128, lot PC218).
5) Phototoxicity study in rats (# 129, lot PC218).
6) Study of threshold illuminance required for Photofrin induced phototoxicity in rats (#138, lot PC218).
7) Duration of photosensitivity in rats following Photofrin administration (#139, lot PC218).
8) Acute toxicity and phototoxicity of aged Photofrin in mice and rats (# 140 and 141, lot PC233 expired).
9) 13 week intravenous toxicity in rats (# 132, lot 86048 and PC 233).
10) 90 day toxicity study in dogs (# 134 and 133, lot PC 225 and PC 229).
11) Microbial mutagenicity test on Photofrin using Ames/Salmonella and E. coli assay (# 170).
12) Microbial mutagenicity test on Photofrin in the presence of illumination (# 169).
13) Rat segment II study (# 165).
14) Rabbit Segment II study (# 166).

III) Mutagenic potential of Photofrin was reviewed in October 1992 by Dr. A.W. Coulter.

1) Sister Chromatid Exchange (# 179).
2) Effects on DNA (#182).
3) Mutagenicity at the tk locus in mouse L51784Y cells (#176).
4) Single dose intravascular tolerance in rabbits (#144)

IV) Studies Reviewed by Dr. Anwar Goheer on Feb. 25, 1993.

1) Primary ocular irritation in rabbits (# 142, lot PC256C).
2) Primary dermal irritation in rabbits (# 143, lot PC256C).
3) In vitro human blood compatibility (# 154, lot PC256C).
4) Comparison of formulations in dogs (# 153, lot 6894B15AL &PC274JS).

V) Studies Reviewed by Dr. Anwar Goheer on Nov. 4, 1993.

Pharmacology/Toxicology

1) Photodynamic therapy for experimental tumors using Photofrin and excimer dye laser (#52).
2) General pharmacology studies (# 120).
3) Fundamental studies on the tumor-localizing properties of Photofrin in hamsters (# 36).
4) Single dose intravenous toxicity of CL 184,116 (Photofrin) in dogs (# 130, lot B90-120-0048).
5) An irritation study of CL 184,116 (Photofrin) administered intra-muscularly in rabbits (# 146, lot B90-120-0045).
6) Study on thrombophlebitis following intravenous injection of CL 184,116 (Photofrin) in rabbits (#145, lot B90-120-0048)
7) Hemolytic effects on human erythrocytes of CL 184,116 (Photofrin) with or without light illuminance (#155, Lot PC256C)
8) Correspondence to Photofrin file dated September 28, 1992. Hemolytic potential of Photofrin (#156, lot PC256C)
9) Antigenicity study of Photofrin (CL 184,116) antibody production in mice (#148 and 149, lot B90-120-0048L).
10) Antigenicity study of Photofrin (CL 184,116); active systemic anaphylaxis in guinea pigs (# 150, Lot B90-120-0048L).
11) Immuno-pharmacology studies in vitro on a porphyrin derivative (Photofrin) used in photodynamic therapy (# 151, lot unknown).
12) Experimental studies of immuno-toxicity of a photosensitizing agent (Photofrin) in mice (#152, lot unknown).
13) Reproductive toxicity of CL 184,116 (Photofrin) administered intravenously prior to and in the early stages of pregnancy in rats (#164).
14) Reproduction study of CL 184,116 (Photofrin) administered intravenously during perinatal and lactation periods in rats (# 167 and 168).

B) Pharmacokinetics

1) Pharmacokinetic studies of Photofrin in the rat (# 222).
2) Fundamental studies on the tumor-localizing properties of Photofrin (# 36).
3) Pharmacokinetic studies of Photofrin in the dog (#223).

VI Reviewed by Dr. W. D. McGuinn for IND

113) Abramson A, *et al.* The pathologic effects of photodynamic therapy on the larynx. *Arch Otolaryngol Head Neck Surg.* 1988;114:33-39.

Studies Reviewed in this Submission:

Pharmacology

1) Girotti AW. Photodynamic action of protoporphyrin IX on human erythrocytes: cross linking of membrane proteins. *Biochem. Biophys. Res. Commun.* 1976; 72:1367-1374.
2) Kessel D. Effects of photoactivated porphyrins at the cell surface of leukemia L1210 cells. *Biochemistry.* 1977;16:3443-3449.
3) Biade S. *et al.* Photosensitization by Photofrin II delivered to W126VA4 SV40-transformed human fibroblasts by low density lipoproteins: inhibition of lipid synthesis and fatty acid uptake. *Photochem Photobiol.* 1992; 55:55-61.
4) Klaunig JE *et al.* Morphologic studies of bladder tumors treated with hematoporphyrin derivative photochemotherapy. *Am. J. Pathol.* 1985: 119: 236-243.
5) Gibson S. *et al.* Evidence against the production of superoxide by photo-irradiation of hematoporphyrin derivative. *Photochem. Photobiol.* 1984: 40:441-448.
6) Sporn LA, Foster TH. Photofrin and light induces microtubule depolymerization in cultured human endothelial cells. *Cancer Res.* 1992; 52:3443-3448.
9) Gomer C. DNA damage and repair in CHO cells following hematoporphyrin photoradiation. *Cancer Lett0ers.* 1980; 11:161-167.
10) Blazek E and Hariharan P. Alkaline elution studies of hematoporphyrin derivative photosensitized DNA damage and repair in Chinese hamster ovary cells. *Photochem. Photobiol.* 1984: 40(1): 5-13.
11) Boehgeim J. *et al.* Nucleic acid damage in L929 murine fibroblasts induced by HPD. In: Jori and Perria, eds. *Photodynamic Therapy of Tumors and Other Diseases.* Padova, Spain: Libreria Progette Editore; 1985: 133-136.
15) Berg K and Moan J. Photodynamic effects of Photofrin II on cell division in human NHIK 3025 cells. *Int J Radiat Biol.* 1988; 53:(5):797-811.
16) Lee See K *et al.* Oxygen dependency of photocytotoxicity with heamatoporphyrin derivative. *Photochem. Photobiol.* 1984; 39:631-634.
20) Gomer C and Razum N. Acute skin response in albino mice following porphyrin photosensitization under oxic and anoxic conditions. *Photochem Photobiol.* 1984; 40(4):435-439.

21) Weishaupt K *et al.* Identification of singlet oxygen as the cytotoxic agent in photo-inactivation of human cells in vitro in the presence of heamatoporphyrin. *Br J Cancer.* 1979; **39**:398-407.

26) Athar M *et al. In situ* evidence for the involvement of superoxide anions in cutaneous porphyrin photo-sensitization. *Biochem. Biophys Res. Commun.* 1988; **151**(3):1054-1059.

28) Hiharan PV *et al.* Production of hydroxyl radicals in cell systems exposed to haematoporphyrin and red light. *Int J Radiat Biol.* 1980; **37**(6): 691-694.

29) Athar M *et al.* A novel mechanism for the generation of superoxide anions in hematoporphyrin derivative-mediated cutaneous photo-sensitization. *J Clin Invest.* 1989;**83**:1137-1143.

30) McLear PW and Hayden RE. Prevention of cutaneous phototoxicity in photodynamic therapy. *Am J Otolaryngol.* 1989; **10**:92-98.

50) Shulock J *et al.* Cellular effects of hematoporphyrin derivative photodynamic therapy on normal and neoplastic rat bladder cells. *Am J Pathol.* 1986; **122**:277-283.

52) Tahaka M *et al.* Photodynamic therapy for experimental tumors using Photfrin II and excimer dye laser. Lederle (Japan) Ltd, Shiki Laboratories, Japan: 1992; 1-15.

64) Cho YH, *et al.* Effects of photodynamic therapy in combination with intravesical drugs in a murine bladder tumor. *J Urol.* 1992; **147**:743-746.

67) Cowled PA, Forbes IJ. Photocytotoxicity in vivo of haematoporphyrin derivative components. *Cancer Letters.* 1985; **28**:111-118.

68) Cowled PA, *et al.* Potentiation of photodynamic therapy with haematoporphyrin derivatives by glucocorticoids. *Cancer Letters.* 1985; **29**:107-114.

72) Okunaka T, *et al.* A comparison between argon-dye and excimer-dye laser for photodynamic effect in transplanted mouse tumor. *Jpn J Cancer Res.* 1992; **83**:226-231.

77) Nelson JS, *et al.* Use of multiple photosensitizers and wavelengths during photodynamic therapy: a new approach to enhance tumor eradication. *J Natl Cancer Inst.* 1990; **82**:868-873.

81) Nelson JS, *et al.* Glucose administration combined with photodynamic therapy of cancer improves therapeutic efficacy. *Lasers Surg Med.* 1992; **12**:153-158.

95) Ma LW, *et al.* Effect of mitomycin C on the uptake of Photofrin II in a human colon adenocarcinoma cell line. *Cancer Letters.* 1992; **64**:155-162.

98) Gonzalez S, *et al.* Treatment of Dunning R3327-AT rat prostate tumors with photodynamic therapy in combination with misonidazole. *Cancer Res.* 1986; **46**:2858-2862.

99) Santus R, *et al.* Protection against light-activated Photofrin II killing tumor cells by nitroimidazoles. *Radiat Res.* 1992; **130**:31-37.

101) Foultier M-T, *et al.* Photodynamic treatment of normal endothelial cells or glioma cells in vitro. *Surg Neurol.* 1992; **37**:83-88.

102) Ben-Hur E, *et al.* Protection by the fluoride ion against phthalocyanine-induced photodynamic killing of Chinese hamster cells. *Photochem Photobiol.* 1992; **55**:231-237.

104) Purkiss SF, *et al. In vitro* modulation of haematoporphyrin derivative photodynamic therapy on colorectal carcinoma multicellular spheroids by verapamil. *Br J Surg.* 1992; **79**:120-125.

108) Boyle D, and Potter W. Photobleaching of Photofrin II as a means of eliminating skin photosensitivity. *Photochem Photobiol.* 1987; **46**(6):997-1001.

116) Shikowitz M. Comparison of pulsed and continuous wave light in photodynamic therapy of papillomas: an experimental study. *Laryngoscope.* 1992; **102**:300-310.

122) Hunt DWC, *et al.* Photofrin, but not benzoporphyrin derivative, stimulates hematopoiesis in the mouse. *Immunopharmacology.* 1993; **26**:203-212.

225) Perry RR, *et al.* Intravenous vs. intraperitoneal sensitizer: Implications for intraperitoneal photodynamic therapy. *Photochem Photobiol.* 1991; **53**(3):335-340.

229) Fingar VH, *et al.* The effects of thromboxane inhibitors on the microvascular and tumor response to photodynamic therapy. *Photochem Photobiol.* 1993; **58**:393-399.
230) Taber SW, *et al.* The effects of aspirin on microvasculature after photodynamic therapy. *Photochem Photobiol.* 1993; **57**:856-861.
240) Everson JF, *et al.* Tumor-localizing and photosensitizing properties of the main component of Hematoporphyrin Derivative. *Cancer Res.* 1984, **44**:482-486.

Toxicology

32) Farrario A and Gomer CJ. Systemic toxicity in mice induced by localized porphyrin photodynamic therapy. *Cancer Res.* 1990; **50**:539-543.
41) Star W *et al.* Destruction of rat mammary tumor and normal tissue microcirculation by hematoporphyrin derivative photo radiation observed in vivo in sandwich observation chambers. *Cancer Res.* 1986; **46**:2532-2540.
85) Zhou C, *et al.* The biological effects of photodynamic therapy on normal skin in mice - I. A light microscopic study. *Adv Exp Med Biol.* 1985; **93**:105-109.
86) Zhou C, *et al.* The biological effects of photodynamic therapy on normal skin in mice - II. An electron microscopic study. *Adv Exp Med Biol.* 1985; **93**:111-115.
107) Gomer C, *et al.* Hematoporphyrin derivative photoradiation therapy for the treatment of intraocular tumors: examination of acute normal ocular tissue toxicity. *Cancer Res.* 1983; **43**:721-727.
110) Stewart Fa, *et al.* Functional and histological damage in the mouse bladder after photodynamic therapy. *Br J Cancer.* 1992; **65**:884-890.
111) Yoshida Y, *et al.* Photoactivated Photofrin II: astrocytic swelling precedes endothelial injury in rat brain. *j Neuropathol Exp Neurol.* 1992; **51**:91-100.
117) Wirtschafter JD, *et al.* Severe but temporary injury to rabbit orbicularis oculli muscle using dihematoporphyrin ether and laser photochemomyectomy. *Movement Disorders.* 1992; **7**:171-177.

Genotoxicity

175) Gomer C, *et al.* Transformation and mutagenic potential of porphyrin photodynamic therapy in mammalian cells. *Int J Radiat Biol.* 1988; **53**(4):651-660.

181) Kvam E, *et al.* The lengths of DNA fragments light-induced in the presence of a photosensitizer localized at the nuclear membrane of human cells. *Biochim Biophys Acta.* 1990; **1049**:33-37.

185) Tan JC, *et al.* Effects of radiation and porphyrin on mitosis and chromosomes in human hematopoietic cell lines. *J Med.* 1976; 7(2):169-176.

Reproductive Toxicity

No new reproductive toxicity studies were submitted with this NDA

ADME

35) Kongshaug M *et al.* Distribution of porphyrins with different tumor localizing ability among human plasma proteins. *Brit J Cancer.* 1989; **59**:184-188.

38) Bugelski P *et al.* Autoradiographic distribution of hematoporphyrin derivative in normal and tumor tissue of the mouse. *Cancer Res.* 1981; **41**:4606-4612.

58) Woodburn KW et al. Evaluation of tumour and tissue distribution of porphyrins for use in photodynamic therapy. Br J Cancer. 1992; **65**:321-328.

59) Baumgartner R *et al.* Pharmacokinetics of fluorescent polyporphyrin Photofrin II in normal rat tissue and rat bladder tumor. *Photochem Photobiol* 1992; **55**:569-574.

121) Belliner DA, *et al.* Distribution and elimination of Photofrin II in mice. *Photochem Photobiol.* 1989; **50**(2):221-228.

206) Sabben G, *et al.* Time dependence of 3H-hematoporphyrin derivative distribution in the digestive tract in the rat. In: Andreoni A, Cubeddu R, eds. *Porphyrins in Tumor Phototherapy.* New York, NY: Plenum Press; 1984:243-245.

207) Pantelides M, *et al.* A comparison of serum kinetics and tissue distribution of Photofrin II following intravenous and intraperitoneal injection in the mouse. *Photochem Photobiol.* 1989; **49**(1):67-70.

208) Belliner DA, *et al.* Distribution and elimination of Photofrin II in mice. *Photochem Photobiol.* 1989; **50**(2):221-228. Note same as reference # 121.

211) Hara N, *et al.* Distribution of hematoporphyrin derivative in normal and malignant tissue. *Jpn J Exp Med.* 1988; **58**(3):139-143.

212) Kaye AH, *et al.* Uptake and retention of hematoporphyrin derivative in an *in vivo/in vitro* model of cerebral glioma. *Neurosurgery.* 1985; **17**:883-890.

213) Carpanini BA, *et al.* Uptake and localisation of haematoporphyrin derivative in normal rat liver. *Biochem Pharmacol.* 1987; **36**(17):2759-2764.

219) Bjorkman DJ, *et al.* Photofrin II localization in rat cecum. *Laser Surg Med.* 1989; **9**:286-289.

226) Ma LW, *et al.* Effects of light exposure on the uptake of Photofrin II in tumors and normal tissues. *Int J Cancer.* 1992; **52**:120-123.

Studies Not Reviewed:

7) Torinuki W *et al.* Lysosome destruction and lipoperoxide formation due to active oxygen generated from haematoporphyrin and UV irradiation. *Br J Dermatol.* 1980; **102**:17-27.

8) Hampton JA and Selman SH. Mechanisms of cell killing in photodynamic therapy using a novel *in vivo/in vitro* light culture system. *Photochem Photobiol.* 1992: **56**:235-243.

12) Fiel R et al. Introduction of DNA damage by porphyrin photosensitizers. *Cancer Res.* 1981; **41**: 3543-3545.

13) Moan J *et al.* DNA single strand breaks and sister chromatid exchanges induced by treatment with hematoporphyrin & light or by X-rays in human NHIK 3025 cells. *Cancer Res.* 1980; **40**:2915-2918.

14) Evensen J and Moan J. Photodynamic action and chromasomal damage: a comparison of haematoporphyrin derivative (HPD) and light with X-irradiation. *Br J Cancer.* 1982; **45**:456-465.

17) Moan J and Sommer S. Oxygen dependence of the photosensitizing effects of hematoporphyrin derivative in NHIK 3025 cells. *Cancer Res* 1985; **45**:1608-1610.

18) Mitchel J *et al.* Oxygen dependence of hematoporphyrin derivative-induced photoinactivation of Chinese hamster cells. *Cancer Res.* 1985; **45**:2008-2011.

19) Spikes JD. Quantum yields and kinetics of the photobleaching of hematoporphyrin, Photofrin II, tetra-(4-sulfonatophenyl)-porphine and uroporphyrin. *Photochem Photobiol.* 1992; **55**: 797-808.

22) Moan J *et al.* The mechanism of photodynamic inactivation of human cells in vitro in the presence of haematoporphyrin. *Br J Cancer.* 1979; **39**:398-407.

23) Tatsuta M *et al.* Photodynamic effects of exposure to hematoporphyrin derivatives and dye laser radiation on human gastric adenocarcinoma cells. *J Natl Cancer Inst.* 1984; 73:59-67.

25) Peterson DA *et al.* A hypothesis for the molecular mechanism of tumor killing by porphyrins and light. *Med Hypotheses.* 1981: 7:201-205.

27) Lee-See K *et al.* Hydroxyl radical production by haematoporphyrin derivative. *Aust Soc Med Res.* 1985;127. Abstract.

31) Kerdel F *et al.* In vivo mediator release and degranulation of mast cells in hematoporphyrin derivative- induced phototoxicity in mice. *J Invest Dermatol.* 1987; 88:277-280.

33) Wilson BC and Patterson MS. The physics of photodynamic therapy. *Phys Med Biol.* 1986; 31:327-360.

34) Kongshaug M. Distribution of tetrapyrrole photosentizers amoung human plasma proteins. *Int J Biochem* 1992; 24:1239-1265. A review.

37) Roberts WG and Hasan T. Role of neovasculature and vascular permeability on the tumor retention pf photodynamic agents. *Cancer Res.* 1992; 52:924-930.

39) Kreimer-Birnbaum M *et al.* Studies with hematoporphyrin derivative in transplantable urothelial tumors. In: Andreoni AS, Cubeddu R, eds. Porphyrins in Tumor Phototherapy. New York. NY: Plenum Press; 1984:235-241.

40) Selmal S *et al.* Blood flow in transplantable bladder tumors treated with hematoporphyrin derivative and light. *Cancer Res.* 1984; 44:1924-1927.

42) Selman SH *et al.* Hematoporphyrin derivative photochemotherapy of experimental bladder tumors. *J Urol.* 1985; 133:330-333.

43) Fingar V and Henderson B. Drug and light dose dependence of photodynamic therapy: a study of tumor and normal tissue response. *Photochem Photobiol.* 1987: 46(5):837-841.

44) Moore RB *et al.* Non-invasive nonitoring of photodynamic therapy with 99Technetium HMPAO scintigraphy. *Br J Cancer* 1992; 65:491-497.

45) Reed *et al.* The effect of photodynamic therapy on the microcirculation. *J Surg Res.* 1988; 45:452-459.

46) Kozlov VI *et al.* Blood microcirculation under photodynamic process. *J Clin Laser Med and Surg.* 1992(April);95-103.

47) Fingar VH *et al.* The effects of thromboxane inhibitors on vessel constriction, vessel leakage, and tumor response in photodynamic therapy. *Photochem Photobiol* 1992;55(Suppl)55S (Abs SS-04-3).

48) Chang C and Dougherty T. Photoradiation therapy: Kinetics and thermodynamics of porphyrin uptake and loss in normal and malignant cells in cultrue. *Radiat Res.* 1984;74:498. Abstract.

49) Henderson B *et al.* Aspects of the cellular uptake and retention of hematoporphyrin derivative and their correlation with the biological response to PRT in vitro. *Adv Exp Med Biol.* 1983. ; 160:129-138.

51) Nelson J *et al.* Nechanism of tumor destruction following photodynamic therapy with hematophorphyrin derivative, chlorin and phthalocyanine. *J Natl Cancer Inst.* 1988; 80:1599-1605.

53) Bellnier D et al. Effects of 514.5-nm argon ion laser radiation on hematoporphyrin derivative-treated bladder tumor cells In Vitro and In Vivo J Natl Cancer Inst. 1985; 74:617-625.

54) van Gemert JC *et al.* Wavelength and light-dose dependence in tumour phototherapy with haematoporphyrin derivative. *Br J Cancer.* 1985; 52:43-49.

55) Gomer CJ *et al.* Action spectrum (620-640 nm) for hematoporphyrin derivative induced cell killing. *Photochem Photobiol.* 1984; **39**:365-368.
56) Moan J and Berg K. Photochemotherapy of cancer: experimental research. *Photochem Photobiol.* 1992; **29**:142-154.
57) Spinelle P and Dal Fante M. Photodynamic therapy of solid tumors. *Seminars in Hematol.* 1992; **29**:142-154.
60) Moore J *et al.* Dose-response relationships for photodynamic injury to murine skin. *Br J Radiol.* 1986; **59**:257-261.
61) Finger VH, *et al.* Modification of photodynamic therapy-induced hypoxia by Fluosol-DA (20%) and carbogen breathing in mice. *Cancer Res.* 1988;**48**(12):3350-3354.
62) Bellnier DA, *et al.* Hematoporphyrin derivative and pulse laser photoradiation. In: Doiron DR, Gomer CJ eds. *Porphyrin Localization and Treatment of Tumors.* New York, NY: Alan R Liss Inc; 1984: 533-540.
63) Kelly J, *et al.* Photodynamic destruction of human bladder carcinoma. *Br J Cancer,* 1975; **31**:237-244.
65) Nseyo UO, *et al.* Experimental photodynamic treatment of canine bladder. *J Urol.* 1985; **133**:311-315.
66) Nseyo UO, *et al.* Study factors mediating effect of photodynamic therapy on bladder in canine bladder model. *Urology.* 1988; **32**(1):41-45.
69) Ellingsen R, *et al.* Photoradiation therapy of Lewis lung tumors in mice with low optical dose rate and high HPD-dose. In: Doiron DR, Gomer CJ, eds. *Porphyrin Localization and Treatment of Tumors.* New York, NY: Alan R Liss Inc; 1984; 647-655.
70) Hayata Y, *et al.* Fiberoptic bronchoscopic photoradiation in experimentally induced canine lung cancer. *Cancer.* 1983; **51**:50-56.
71) Tochner Z, *et al.* Treatment of murine intraperitoneal ovarian ascitic tumor with hematoporphyrin derivative and laser light. *Cancer Res.* 1985; **45**:2983-2987.
73) Boyle RW, *et al.* Biological activities of phthalocyanines XIV. Effect of hydrophobic phthalimidomethyl groups on the in vivo phototoxicity and mechanism of photodynamic action of sulphonated aluminum phthalocyanines. *Br J Cancer.* 1992; **65**:813-817.
74) Marijnissen JPA, *et al.* Tumor and normal tissue response to interstitial photodynamic therapy of the rat R-1 rhabdomyosarcoma. *Int J Rad Oncol Biol Phys.* 1992; **22**:963-972.
75) Winther J. Effect of Photofrin II and light energy on retinoblastoma-like cells in vitro. Dose-response relationships, effect of light dose rate and recovery ratio. *J Cancer Res Clin Ocol.* 1989; **115**(1):73-78.
76) Bruce RA. Evaluation of hematoporphyrin photoradiation therapy to treat choroidal melanomas. *Lasers Surg Med.* 1984;**4**:59-64.
78) Cheli R, *et al.* HPD phototherapy on spontaneous tumors in dog and cat. In: Andreoni A, and Cubeddu R, eds. *Porphyrins in Tumor Phototherapy.* New York, NY, Plenum Press; 1984:251-257.
79) Cheli R, *et al.* Hematoporphyrin derivative photochemotherapy of spontaneous animal tumors: clinical results with optimized drug dose. *Cancer Letters.* 1984; **23**:61-66.
80) Dougherty TJ, *et al.* Interstitial photoradiation therapy for primary solid tumors in pet cats and dogs. *Cancer Res.* 1981; **41**:401-404.
82) Bottiroli G, *et al.* Distribution of di-sulfonated aluminum phthalocyanine and Photofrin II in living cells: a comparative fluorometric study. *Photochem Photobiol.* 1992; **55**:575-585.
83) Dellinger M, Brault D. Uptake and retention of Photofrin by cultivated human lymphoblastic cells

(Reh6): preferential affinity of the cells for a minor component demonstrated by normal phase chromatography. *Photochem Photobiol.* 1992; **55**:587-594.

84) Okunaka T, Eckhauser ML, Kato H, *et al.* Correlation between photodynamic efficacy of differing porphyrins and membrane partitioning behavior. *Lasers Surg Med.* 1992; **55**:98-103.

87) Roberts WG, and Berns MW. In vitro photosensitization I. Cellular uptake and subcellular localization of mono-L-aspartylchlorin e_6, chloro-aluminum sulfonated phthalocyanine and Photofrin II. *Lasers Surg Med.* 1989; **9**:90-101.

88) Fu N-W, *et al.* Photosensitization of mitochondrial adenosine-triphosphatase and adenylate kinase by hematoporphyrin derivative in vitro. In: Kessel D, ed. *Methods in Porphyrin Photosensitization.* New York, NY: Plenum Press; 1985:161-167.

89) Merlin J-L, *et al.* MTT assays allow quick and reliable measurement of the response of human tumour cells to photodynamic therapy. *Eur J Cancer.* 1992; **28A**:1452-1458.

90) Roberts WG, *et al.* In vitro photosensitization II. An electron microscopy study of cellular destruction with mono-L-aspartyl chlorin e and Photofrin II. *Lasers Surg Med.* 1989; **9**:102-108.

91) Penning LC, *et al.* Activation of cyclooxygenase after HPD-photosensitization of T24 human bladder transitional carcinoma cells *in vitro*. *Photochem Photobiol.* 1992; **55**(Suppl):56S (Abs SS-04-5).

92) Evans S, *et al.* Effect of photodynamic therapy on tumor necrosis factor production my murine nacrophages. *J Natl Cancer Inst.* 1990; **82**(2):34-39.

93) Nseyo UO, *et al.* Urinary cytokines following photodynamic therapy for bladder cancer. A preliminary report. *Urology.* 1990; **36**(2):167-171.

94) Henderson BW, and Belliner DA. Tissue localization of photosensitizers and the mechanism of photodynamic tissue destruction. In: *Photosensitizing Compounds: Their Chemistry, Biology and Clinical Use* (Ciba Foundatioin Symposium 146). Chichester: Wiley. 1989; 112-130.

96) Yamamoto N, *et al.* Photodynamic immunopotentiation: *in vitro* activation of macrophages by treatment of mouse peritoneal cells with haematoporphyrin derivative and light. *Eur J Cancer.* 1991; **27**(4):467-471.

97) Fingar V. Modification of PDT tumor response by Fluosol-DA 20%. *Lasers Surg Med.* 1986;6:236.Abstract 238.

100) Prinsze C, *et al.* Interaction of photodynamic treatment and either hyperthermia or ionizing radiation and of ionizing radiation and hyperthermia with respect to cell killing of L929 fibroblasts, Chinese hamster ovary cells and T24 human bladder carcinoma cells. *Cancer Res.* 1992; **52**:117-120.

103) West CML, Moore JV. Mechanisms behind the resistence of spheroids to photodynamic treatment: a flow cytometry study. *Photochem Photobiol.* 1992; **55**:425-430.

105) Selman S, *et al.* Jejunal blood flow after exposure to light in rats injected with hematoporphyrin derivative. *Cancer Res.* 1985; **45**:6425-6427.

106) Chaudhuri K, *et al.* Histological study of the effect of hematoporphyrin derivative photodynamic therapy on the rat jejunum. *Cancer Res.* 1986; **46**:2950-2953.

109) Carter R, *et al.* Splanchnic vascular changes in response to intragepatic and extrahepatic tumour. *Br J Cancer.* 1992; **79**:453 (Abstract).

112) Pelton JJ, *et al.* Intrathoracic organ injury associated with photodynamic therapy. *J Thoracic Cardiovasc Surg.* 1992; **103**:1218-1223.

114) Yamamoto N, *et al.* Tumoricidal capacities of macrophages photodynamically activated with hematoporphyrin derivative. *Photochem Photobiol.* 1992; **56**:245-250.

115) Mirando WS, *et al.* UVB radiation and photosensitizers plus light promote monocyte

antimicrobial activities. *Clin Res.* 1992; 40:541A.
127) Dougherty T. Photodynamic therapy (PDT) of malignant tumors. *CRC Critical Rev Oncol Hematol.* 1984; 2:83-116.

177) Evans HE, *et al.* Cytotoxic and mutagenic effects of the photodynamic action of chloroaluminum phthalocyanine and visible light in L5178Y cells. *Photochem Photobiol.* 1989; 49(1):43-47.
178) Hozier J, *et al.* Chromosome 11 aberrations in small colony L5178Y TK-/-mutants early in their clonal history. *Mutat Res.* 1985; 147:237-242.
180) Kvam E, Moan J. A comparison of three photosensitizers with respect to efficiency of cell inactivation, fluorescence quantum yield and DNA strand breaks. *Photochem Photobiol.* 1990; 52:769-773.
183) Gomer CJ, *et al.* Comparison of mutagenicity and induction of sister chromatid exchange in Chinese hamster cells exposed to hematoporphyrin derivative photoradiation, ionizing radiation, or ultraviolet radiation. *Cancer Res.* 1983; 43:2622-2627.
184) Breimer LH. Molecular mechanisms of oxygen radical carcinogenesis and mutagenesis: the role of DNA base damage. *Molec. Carcinogen.* 1990; 3:188-197.
186) Hazen MJ, *et al.* Induction of sister chromatid exchanges in *allium cepa* meristematic cells exposed to *meso*-Tetra(4-pyridyl) porphine and hematoporphyrin photoradiation. *Photochem Photobiol.* 1987; 46(4):463-467.
187) McFee AF, Sherrill MN. Species variation in BrdUrd-induced sister-chromatid exchanges. *Mutat Res.* 1979; 62:131-138.
188) Natarajan AT, *et al.* Influence of incorporated 5-bromodeoxyuridine on the frequencies of spontaneous and induced sister-chromatid exchanges, detected by immunological methods. *Mutat Res.* 1986; 163:51-55.
189) Gutter B, *et al.* The photodynamic modification of DNA by hematoporphyrin. *Biochim Biophys Acta.* 1977; 475:307-314.
190) Moan J, *et al.* Photodynamic effects on human cells exposed to light in the presence of hematoporphyrin. pH effects. *Cancer Letters* 1980; 9:327-331.
191) Boegheim J, *et al.* Photodynamic effects of haematoporphyrin derivative on DNA repair in murine L929 fibroblasts. *Biochem J.* 1987; 244:711-715.
192) Boye E and Moan J. The photodynamic effect of hematoporphyrin on DNA. *Photochem Photobiol.* 1980; 31:223-228.

193) Kawanishi S, *et al.* Photodynamic guanine modification by hematoporphyrin is specific for single-stranded DNA with singlet oxygen as a mediator. *J Biol Chem.* 1986; **261**:6090-6095.
194) Boegheim JPJ, *et al.* Photodynamic effects of hematoporphyrin-derivative on enzyme activities of murine L929 fibroblasts. *J Photochem Photobiol.* 1987; **1**:61-73.
196) Gomer CJ. Preclinical examination of first and second generation photosensitizers used in photodynamic therapy. *Photochem Photobiol.* 1991; **54**:1093-1107.
197) Henderson BW, Miller AC. Effects of scavengers of reactive oxygen and radical species on cell survival following photodynamic treatment *in vitro*: comparison to ionizing radiation. *Radiat Res.* 1986; **108**:196-205.
198) Moan J, *et al.* Fluorescence and photodynamic effects of phthalocyanines and porphyrins in cells. In: Henderson BW, Dougherty TJ, eds. *Photodynamic Therapy. Basic Principles and Clinical Applications.* New York, NY: Marcel Dekker Inc; 1992:19-36.
199) Rydberg B. The rate of strand separation in alkali of DNA of irradiated mammalian cells. *Radiat Res.* 1975; **61**:274-287.
200) Sastry KS, Gordon MP. The photosensitized degradation of guanosine by acridine orange. *Biochim Biophys Acta.* 1966; **129**:42-48.
201) Schneider JE, *et al.* Methylene blue plus light mediates 8-hydroxy-2'-deoxyguanosine formation in DNA preferentially over strand breakage. *Nucleic Acids Res.* 1990; **18**:631-635.
202) Simon MI, Van Vunais H. The photodynamic reaction of methylene blue with deoxyribonucleic acid. *J Mol Biol.* 1962; **4**:488-499.
203) Speck WT, *et al. In Vitro* studies of effects of light an driboflavin on DNA an dHeLa Cells. *Pediat Res.* 1975; **9**:150-153.
204) Williams GM. Methods for evaluating chemical genotoxicity. *Annu Rev Pharmacol Toxicol.* 1989;**29**:189-211.
205) Williams GM, Weisburger JH. Chemical carcinogenesis. In: Amdur MO, Doull J, Klaassen CD, eds. *Casarett and Doull's Toxicology. The Basic Science of Poisons,* 4th ed. New York, NY: Pergamon Press; 1991:127-200.
209) Gomer C, Dougherty T. Determination of [^{3}H]- and [^{14}C] hematoporphyrin derivative distribution in malignant and normal tissue. *Cancer Res.* 1979; **39**:146-151.
210) Gomer C, *et al.* Tissue distribution of 3H-hematoporphyrin derivative in athymic "nude" mice heterotransplanted with human retinoblastoma. *Invest Ophthalmol Vis Sci.* 1982; **22**(1):118-120.
214) Boggan J, *et al.* Hematoporphyrin derivative photoradiation therapy of the rat 9L gliosarcoma brain tumor model. *Laser Surg Med.* 1984; **4**:99-105.
215) Jeeves W, *et al.* Studies of HPD and radiolabelled HPD *in vivo* and *in vitro* In: Kessel D, ed. *Methods in Porphyrin Photosensitization.* New York, NY. Plenum Press; 1985:51-67.
216) Krohn DL, *et al.* Diagnosis of model choroidal malignant melanoma by hematoporphyrin derivative fluorescence in rabbits. *Invest Ophthalmol.* 1974; **13**:244-255.
217) Elmets CA, *et al.* Photofrin II photodynamic therapy: pharmacokinetics and efficacy in the treatment of chemically-induced skin tumors in mice. *Photochem Photobiol.* 1987; 45(suppl):Abstract 103S.
220) Kessel D, *et al.* Chemical, biologic and biophysical studies on hematoporphyrin derivatives. In: Kessel D, ed. *Methods in Porphyrin Photosensitization.* New York, NY: Plenum Press; 1992: 213-227.
221) Peng Q, *et al.* Sensitizer for photodynamic therapy of cancer: A comparison of the tissue distribution of Photofrin II and aluminum phthalocyanine tetrasulfonate in nude mice bearing a human malignant tumor. *Int J Cancer.* 1991; **48**:258-264.

224) Kessel D. Porphyrin-lipoprotein association as a factor in porphyrin localization. *Cancer Letters.* 1986; 33:183-188.
227) Ji Y, *et al.* Relation between polyporphyrin distribution and blood brain barrier changes in the rat glioma model. *Laser Surg Med.* 1992; 12:174-179.
228) Gomer CJ, *et al.* The effect of localized porphyrin photodynamic therapy on the induction of tumour metastasis. *Br J Cancer.* 1987; 56:27-32.
231) Byrne CJ, *et al.* The chemistry associated with hematoporphyrin derivative (HpD). In: Kessel D, ed. Photodynamic therapy of neoplastic disease, volume II. CRC Press, 1990: 131-143.
232) Brown SB, *et al.* Equilibrium and kinetic studies of the aggregation of porphyrins in aqueous solution. *Biochem J.* 1976; 153:279-285.
233) Turay J, *et al.* Intermolecular association of natural and synthetic water soluble porphyrins. *J Inorg Nucl Chem.* 1978; 40:1687-1690.
234) Margalit R, *et al.* Porphyrin binding and aggregation. In: Kessel D, ed. Photodynamic therapy of neoplastic disease, volume II. CRC Press, 1990:209-223.
235) Dougherty TJ, *et al.* Photoradiation therapy: clinical and drug advances. In: Kessel D and Dougherty TJ, eds. Porphyrin photosensitization, New York: Plenum Press, 1983:3-13.
236) Dougherty TJ, *et al.* Photodynamic sensitizer. In: De Vita V, Hellman S, and Rosenberg S, eds. Principles and practice of oncology. Philadelphia: Lippincott, 1985:2272-2279.
237) Moan J and Sommer S. Action spectra for hematoporphyrin derivative and Photofrin II with respect to sensitization of human cells in vitro to photoinactivation. *Photochem Photobiol.* 1984; 40:631-634.
238) Dougherty TJ and Mang TS. Characterization of intra-tumoral porphyrin following injection of hematoporphyrin derivative or its purified component. *Photochem Photobiol.* 1987; 46:67-70.
239) Foster TH, *et al.* Fluence rate effects in photodynamic therapy of multicell tumor spheroids. *Cancer Res.* 1993; 53:1249-1254.

Portions of this review are excerpted from the sponsors submission.

Reviews

Pharmacology:

1) Girotti AW. Photodynamic action of protoporphyrin IX on human erythrocytes: cross linking of membrane proteins. *Biochem. Biophys. Res. Commun.* 1976; 72:1367-1374.

Five μM Photofrin added to human erythrocytes in suspension caused complete lysis by 24 hours after irradiation with 45 J/cm^2 blue light. SDS-PAGE showed that these cells had decreased concentrations of spectrin. The photodynamic treatment cross-linked many of the intracellular polypeptides. The treatment probably also caused cross-linking of membrane proteins and globin subunits.

2) Kessel D. Effects of photo-activated porphyrins at the cell surface of leukemia L1210 cells. *Biochemistry.* 1977; 16:3443-3449.

A series of synthetic and biological porphyrins destroyed murine leukemia L1210 cells in culture after exposure to light. Cytotoxicity correlated with the aqueous solubility of the porphyrin and binding of the porphyrin to the cell surface. Cytotoxicity did not correlate with mM absorptivity. All porphyrins tested formed singlet oxygen in equal amounts when irradiated. Deutroporphyrin IX was the most cytotoxic com-pound tested. Porphyrin binding to cell surfaces inhibited nucleoside and amino acid transport and 5'-nucleotidase activity. Porphyrin binding also caused changes in cell permeability to actinomycin D and increased binding of the fluorescent probe, a-anilinolnaphthalene sulfonate. Porphyrin binding caused changes in cell surface physiochemistry, measured by partitioning to a PEG layer. The authors conclude that the initial site of photoactivated porphyrin cytotoxicity is the cells surface where these compounds first bind.

3) Biade S. *et al.* Photosensitization by Photofrin II delivered to W126VA4 SV40-transformed human fibroblasts by low density lipoproteins: inhibition of lipid synthesis and fatty acid uptake. *Photochem Photobiol.* 1992; 55:55-61.

These researchers cultured W126VA4 SV40-transformed human fibroblasts with low density lipoproteins containing Photofrin. The cells were then irradiated with 365 nm light. This short wavelength light will cause photoactivation of the Photofrin Soret band as well as the visible bands, thus this study does not model the clinical situation. Photoactivation decreased oleic acid uptake by the cells and inhibited the activity of acyltransferases (measured *in vitro* post treatment). As a consequence of these two effects, the treatment caused near complete inhibition of ^{14}C-oleic acid incorporation into triacylglycerols, cholesteryl esters and phospholipids. Such inhibition would decrease the cells ability to repair damaged membranes.

4) Klaunig JE *et al.* Morphologic studies of bladder tumors treated with hematoporphyrin derivative photochemotherapy. *Am. J. Pathol.* 1985: 119: 236-243.

Klaunig *et al.* initiated transitional cell bladder tumors in male rats by injecting AY27 cells s.c. The rats were treated with Photofrin only, light only, Photofrin plus light, or control. The tumors were irradiated 24 hours after the rats were given Photofrin (590 nm, 200 mW/cm^2*30 min). The researchers sampled tumors with time to 24 hours post PDT and examined tissues by light and electron microscopy.

Control tumors and tumors treated with light only were not damaged. Tumors treated with Photofrin alone showed focal swelling and focal mitochondrial vacuolization in both tumor and normal endothelial cells. In tumors treated with both PDT and Photofrin the cell damage increased with time.

Between 0 and 2 hours tumor cells began to slough into papillary space. Normal endothelial and tumor cells were swollen and vacuoles began to form. Mitochondria were damaged immediately after treatment. Four hours after PDT cells were extensively damaged and mitochondria were destroyed. Endoplasmic reticulum was swollen, polyribosomes disaggregated and the plasma membrane of many cells was blebbing. After 24 hours most of the tumor cells were dead.

5) Gibson S. *et al.* Evidence against the production of superoxide by photo-irradiation of hematoporphyrin derivative. *Photochem. Photobiol.* 1984: 40:441-448.

These investigators reacted hematoporphyrin derivative (HPD) with light in the presence of three superoxide detection systems. These detector reactions were the oxidation of epinephrine to adenochrome, reduction of cytochrome c and reduction of nitro-blue tetrazolium (NBT). The authors compared the ability of HPD to form oxygen radicals to that of known superoxide generating systems. These systems were riboflavin + light and xanthine-xanthine oxidase. They also compared HPD + light to the known singlet oxygen generating system, methylene blue + light. Unlike the known superoxide generators, HPD + light did not reduce cytochrome c or NTB. HPD plus light, but not the superoxide generating systems, could inhibit mitochondrial cytochrome c oxidase activity. The authors conclude that the photosensitization caused by HPD + light is not likely to result from superoxide formation. The similarities between the chemical behavior of HPD + light and the methylene blue + light system implicate singlet oxygen instead.

6) Sporn LA, Foster TH. Photofrin and light induces microtubule depolymerization in cultured human endothelial cells. *Cancer Res.* 1992; 52:3443-3448.

Photofrin PDT caused transient depolymerization of cytoplasmic microtubules (MT) at concentrations of 1 μg/ml in human endothelial cells. MT depolymerization occurred as early as 15 minutes after sublethal light exposure. $[ATP]_{intracellular}$ did not decrease during the depolymerization. MT depolymerization was reversible at low concentrations Photofrin . At higher concentrations irreversible MT depolymerization preceded cell death. The authors postulate that MT depolymerization was secondary to increased $[Ca^{++}]_{intracellular}$ that resulted from photodynamic insult.

9) Gomer C. DNA damage and repair in CHO cells following hematoporphyrin photoradiation. *Cancer Letters.* 1980; 11:161-167.

HPD plus irradiation caused alkali labile lesions and single strand breaks in DNA of CHO cells. This damage was similar in nature to damage caused by X-radiation. Treatments with HPD plus light caused less DNA damage than X-Ray doses that produced equivalent cell survivals. The time the cells required for DNA repair and the extent of that repair was the same for both toxic treatments. Most of the DNA repair occurred within 15 min of the toxic insult and was essentially complete by 30 min.

10) Blazek E and Hariharan P. Alkaline elution studies of hematoporphyrin derivative photosensitized DNA damage and repair in Chinese hamster ovary cells. *Photochem. Photobiol.* 1984: 40 (1): 5-13.

Again HPD plus light caused DNA strand breaks similar to X-radiation. In this study the fractional rate of repair was less for HPD plus light than for X-rays. DNA polymerase inhibitors, cytosine arabinoside and hydroxyurea, suppressed the repair of phototherapy induced strand breaks more strongly than they suppressed repair of X-ray induced breaks. The repair system for phototherapy damage is different from the system that removes pyrimidine dimers after X-ray damage. HPD plus light also caused covalent DNA-protein cross-links.

11) Boehgeim J. *et al.* Nucleic acid damage in L929 murine fibroblasts induced by HPD. In: Jori and Perria, eds. *Photodynamic Therapy of Tumors and Other Diseases.* Padova, Spain: Liberia Progette Editore; 1985: 133-136.

Boehgeim J. *et al.* labeled mouse L929 fibroblasts with ^{14}C-Thymidine. They then incubated these cells with 10 µg/ml HPD. One hour later the cells were irradiated with red light (8 > 590 nm, 4 mW/cm^2). They estimated DNA single strand breaks and DNA protein cross-links by alkaline elution.

HPD +8 caused strand breaks in isolated DNA, thus repair enzymes are not involved in the generation of single strand breaks during illumination. DNA-protein cross-links were not necessary for generation of single strand breaks as with some other anti-tumor drugs. DNA strand breaks did not occur until after 30 min illumination. DNA-protein cross-links began to form immediately and reached a maximum after six hours. Photofrin does not enter the cell nucleus. Damage to DNA and cross-linking is probably caused by radical chain reactions propagating through the cell membranes.

15) Berg K and Moan J. Photodynamic effects of Photofrin II on cell division in human NHIK 3025 cells. *Int J Radiat Biol.* 1988; 53:(5):797-811.

Berg and Moan incubated human NHIK 3025 cells with Photofrin for 18 hours then exposed them to light. Photofrin PDT retarded cells in interphase from entering mitosis. Once this retardation was released the mitotic index increased three fold. This increase was due to a prolongation of metaphase. The researchers observed a 10 fold increase above controls in the number of tripolar mitoses. A two hour wash out did not prevents these mitotic abnormalities.

If the researchers exposed cells to light during mitosis they were delayed from entering anaphase for at least 1 hour. Cells treated during anaphase or telophase entered interphase normally. When the researchers stained cells for b-tubulin 1 hour after PDT, the organization of the spindle apparatus was disturbed. This may explain the metaphase delay and the accumulation of cells in mitosis.

16) Lee See K *et al.* Oxygen dependency of photo-cytotoxicity with haematoporphyrin derivative. *Photochem. Photobiol.* 1984; 39:631-634.

Lee See *et al.* incubated Raji cells (lymphoblastoid B cells a Burkitt's lymphoma) with ^{51}Cr and HPD at varying concentrations. The cells were illuminated with light between 600 and 650 nm at 80 W/m^2. ^{51}Cr release from the cells quantified cytotoxicity. Cytotoxicity increased sigmoidally with light fluence at ambient O_2 tension. When the researchers added dithionite to the cell medium oxygen concentration decreased linearly. Without O_2 cytotoxicity decreased almost to zero, as shown below.

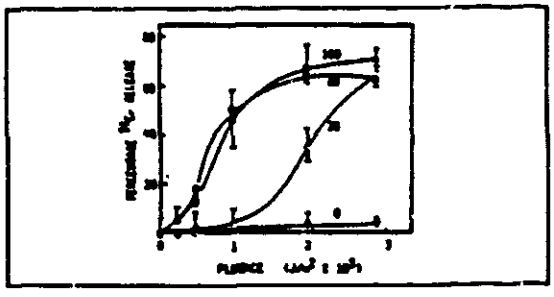


Figure 2. Relationship of ^{51}Cr release to fluence measured at different oxygen concentrations. Cells were incubated with 25 µg/ml HPD. Each point is the mean ± SD of triplicats. – pO_2 160 mm Hg. —— pO_2 80 mm Hg. – 20 mm Hg. – pO 2 0 mm Hg.

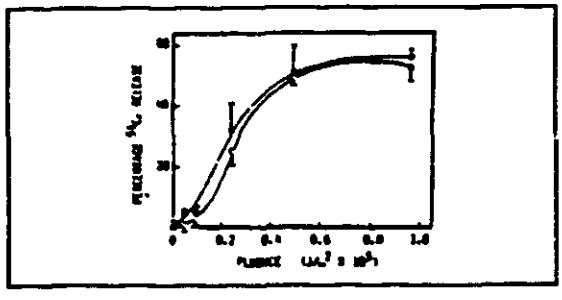


Figure 3. Effect on ^{51}Cr release of adding dithionite to Raji cell suspensions during HPD uptake period. Cells were incubated with 50 µg/ml HPD. – with dithionite. – pO 2 without dithionite.

20) Gomer C and Razum N. Acute skin response in albino mice following porphyrin photosensitization under oxic and anoxic conditions. *Photochem Photobiol.* 1984; 40(4): 435-439.

Gomer and Razum gave Photofrin and HPD to albino mice and quantified damage to normal skin after irradiation. They determined that skin damage caused by PDT with these two compounds was indistinguishable. The authors also restricted oxygen to irradiated mouse skin by clamping off blood flow during irradiation. When tissues were hypoxic prior to PDT, the treatment caused little damage as shown in the following graph. This result supports the hypothesis cell damage caused by PDT is secondary to the generation of oxygen radicals. Nevertheless, it also suggests that PDT will be of little use against hypoxic, slow growing, solid tumors.

HPD (7.5 mg/kg)

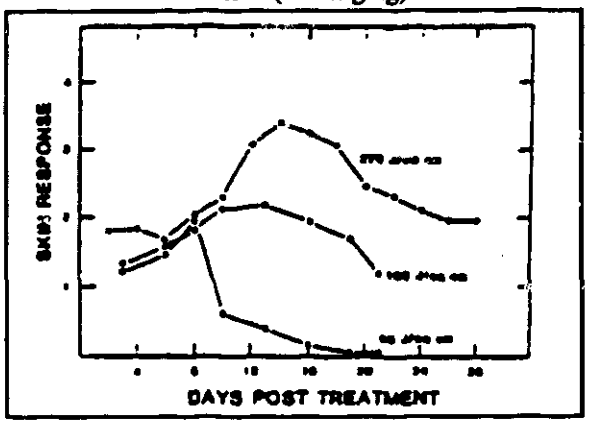


Figure 2. Daily skin response in albino mice injected with HPD (7.5 mg/kg) and exposed to varying total doses of 630 nm light. The dose rate was 150 mW/cm^2 and each point represents the average response in 10-12 mice.

Photofrin II (7.5 mg/kg)

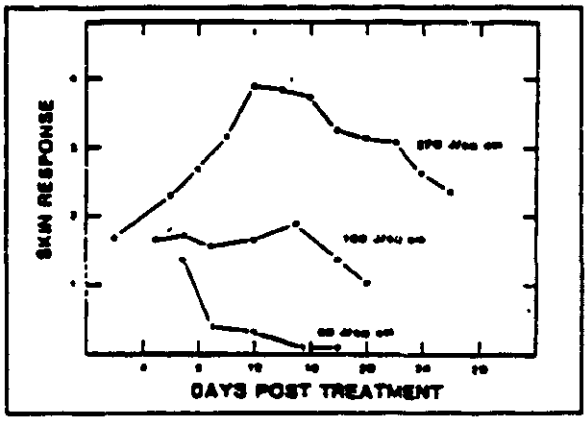


Figure 3. Daily skin response in albino mice injected with Photofrin II (7.5 mg/kg). Other details as per Figure 2.

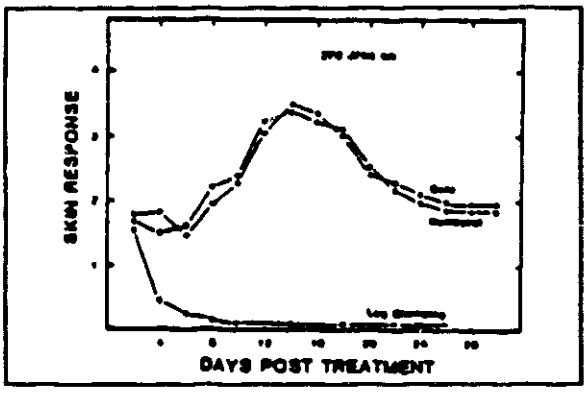


Figure 4. Daily skin response in albino mice injected with HPD (7.5 mg/kg) and exposed to 270 J/cm^2 of 630 nm light delivered at 150 mW/cm2. Mice were treated without anesthesia (Oxic) or while anesthetized (Nembutal). In an additional group the treatment leg was made anoxic (leg clamping) prior to and during treatment. Each point represents the average response in 10-12 mice.

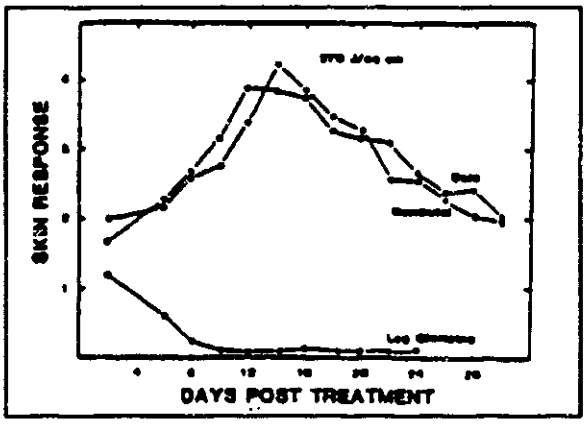


Figure 5. Daily skin response in albino mice injected with Photofrin II (7.5 mg/kg). Other details as per Figure 4.

21) Weishaupt K *et al.* Identification of singlet oxygen as the cytotoxic agent in photo-inactivation of a murine tumor. *Cancer Res.* 1976; 36:2326-2329.

Weishaupt *et al* showed that 1,3-diphenylisobenzofuran, but not furan, completely inhibited the cytotoxicity of HPD-PDT in ascitic TA-3 mouse mammary carcinoma cells. 1,3-diphenylisobenzofuran efficiently traps singlet oxygen to form O-dibenzoylbenzene. This product is formed almost quantitatively in cells receiving HPD-PDT.

26) Athar M *et al. In situ* evidence for the involvement of superoxide anions in cutaneous porphyrin photo-sensitization. *Biochem. Biophys Res. Commun.* 1988; 151(3):1054-1059.

Athar M *et al.* gave Photofrin to mice i.p. 5 mg/kg. Six hours later they irradiated the mice with light at wavelengths >450 nm. This treatment caused the ears of the mice to swell. The researchers assessed photo-sensitization by measuring this ear swelling before and after treatment. The average increase in ear thickness was 217%. Bis[(3,5 diisopropyl-salicylato)(O,O)] copper(II), BDS, mimics superoxide dismutase (SOD) by converting superoxide to hydrogen peroxide. DMSO and b-carotene are radical scavengers. When the researchers gave these chemicals to mice 2 hr before irradiation, ear swelling decreased proportional to dose. This protection increased in the order b-carotene < DMSO < BDS. 0.16 mM/kg (*sic*) BDS inhibited ~ 90% of the swelling.

Sodium diethyldithiocarbamate (DDC) inhibits superoxide dismutase. Hydroxylamine (HA) and 3-amino1,2,4 triazole (ATA) inhibit catalase. These compounds all increased the swelling caused by Photofrin PDT, DDC ~30%, HA ~35% and ATA ~50%. The researchers concluded that PDT caused local tissue damage primarily by generating superoxide ions because BDS, a specific SOD mimic, decreased swelling more than the radical scavengers DMSO and b-carotene.

28) Hariharan PV *et al.* Production of hydroxyl radicals in cell systems exposed to haematoporphyrin and red light. *Int J Radiat Biol.* 1980;37(6): 691-694.

Hydroxyl radicals produce thymine ring saturation products such as 5,6-dihydroxy-dihydrothymine or thymine glycols, in DNA. Hariharan *et al.* measured the concentration of these thymine glycols after Chinese hamster V-79 cells and *Micrococcus radiodurans* were exposed to HPD and light. They concluded that PDT generates hydroxyl radicals.

29) Athar M *et al.* A novel mechanism for the generation of superoxide anions in hematoporphyrin derivative-mediated cutaneous photo-sensitization. *J Clin Invest.* 1989;83:1137-1143.

Again Athar *et al* used ear swelling in mice to assess damage from PDT. In this study allopurinol, an inhibitor of xanthine oxidase, inhibited ~ 90% of the swelling caused by HPD PDT in mice. The authors also showed the presence of superoxide and hydroxyl radicals in mouse skin by ESR. They used 5,5 dimethyl-l-pyrroline N-oxide, DMPO, to trap oxygen centered radicals generated by PDT. Control mouse skin homogenate suspended in buffer, contained no ESR detectable trapped radicals. Allopurinol completely quenched the ESR radical signal. Superoxide dismutase added to the suspension diminished the ESR signal arising from superoxide by ~50%. Catalase also diminished the signal.

Tissue destruction generates abnormally large quantities of purines. Xanthine oxidase converts these excess purines to uric acid. This reaction produces superoxide as a by-product. If insufficient superoxide dismutase is present to scavenge the excess superoxide, the damage to the tissue is compounded. The results of these experiments imply that the superoxide generated by PDT forms as a consequence of excess purine degradation. The superoxide present in the cells need not form by electron transfer from Photofrin.

Tissue destruction also releases Ca^{++} into the cytosol. Excess Ca^{++} can activate calcium

dependant proteases. Ca^{++} dependant proteases cleave xanthine dehydrogenase, a pro-enzyme, to form xanthine oxidase, present only in very low concentrations in the normal cell. Soybean trypsin inhibitor (STI) inhibits the Ca^{++} dependent proteases that cleave xanthine dehydrogenase to form xanthine oxidase. When the authors injected the mice with 320 mg/kg of STI two hours before irradiation, ear swelling diminished by ~60%. Likewise, verapamil, a Ca^{++} channel blocker, administered two hours before irradiation, inhibited ear swelling by ~60%. These results imply that superoxide concentrations increase in damaged tissue because of increased concentrations of xanthine oxidase. High xanthine oxidase concentrations results from the Ca^{++} mediated proteolytic cleavage of xanthine dehydrogenase. Local Ca^{++} concentrations increase as primary PDT damage disrupts cellular membranes and cells leak their contents into the interstitium. This mechanism serves to amplify the damage caused by PDT.

30) McLear PW and Hayden RE. Prevention of cutaneous phototoxicity in photodynamic therapy. *Am J Otolaryngol.* 1989; **10**:92-98.

McLear and Hayden showed that PDT induced damage to rats skin diminished when they gave the rats L-tryptophan and 1,3 diphenylisobenzofuran prophylactically. These compounds scavenge singlet oxygen and other radicals.

50) Shulock J *et al.* Cellular effects of hematoporphyrin derivative photodynamic therapy on normal and neoplastic rat bladder cells. *Am J Pathol.* 1986;**122**:277-283.

Shulock J *et al* determined the cytotoxicity of PDT with HPD in normal (RBL-01) and transition cell carcinoma (AY27) rat bladder cell lines *in vitro*. They varied HPD concentration and measured viability by Trypan blue exclusion. Light exposure was 15 mW/cm^2 for five minutes, a low light dose. Cytotoxicity increased with HPD concentration and with time of exposure to HPD up to 4 hrs. HPD uptake was time dependant and non-linear. The following graph shows that AY-27 tumor cells accumulated about twice the concentration of methanol extractable porphyrin after 48 hours exposure.

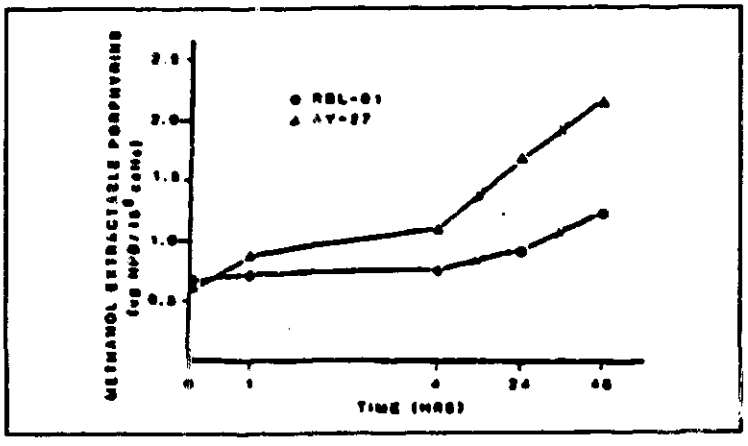


Figure 4. Absorbance of methanol extractable porphyrin (at 395 nm) from RBL-01 and AY27 cells exposed to 25 µg HPD/ml medium in the dark. Values represent the total concentration of methanol extractable porphyrin (µg) per 10^6 cells.

52) Tahaka M *et al.* Photodynamic therapy for experimental tumors using Photofrin II and excimer dye laser. Lederle (Japan) Ltd, Shiki Laboratories, Japan: 1992; 1-15.

Tahaka M *et al* implanted sarcoma 180 cells into the abdominal cavity of ICR mice, Lewis lung carcinoma s.c. in BDF1 mice, human fibrosarcoma HT 180 and human bladder cell carcinoma KK-47 in ICR

nude mice. The mice then received 25 mg/kg Photofrin. The tumors were irradiated with 630 nm pulse laser light at 50 or 100 J/cm^2.

Both light doses killed significant portions of sarcoma 180 tumors but all tumors recovered. The researchers judged five of six mice bearing Lewis lung carcinoma and treated with 100 J/cm^2 tumor free at an unspecified time. They judged four of eight mice treated with 50 J/cm^2 tumor free. The other four died from inflammation secondary to PDT. Photodynamic therapy inhibited Human fibrosarcoma HT-180 and human bladder cell carcinoma KK-47 growth 83 and 78% respectively on day 28 post PDT.

64) Cho YH *et al.* Effects of photodynamic therapy in combination with intravesical drugs in murine bladder tumor. *J Urol.* 1992: 147:743-746.

Cho *et al* implanted MBT-2 FANFT induced murine transitional cell carcinoma cells s.c. in female C3H/He mice. They allowed the tumors to grow to a predetermined size. Then they randomized the mice to groups treated with saline, PDT, thiotepa, adriamycin, mitomycin C, BCG or PDT plus one of the drugs. They then treated the mice with a single dose of one of the four drugs or saline. Forty eight hours later, they injected the mice in the PDT groups with 7.5 mg/kg Photofrin, i.p. Twenty-four hours later they treated the tumors with 200 J/cm^2 laser light. The researchers evaluated these therapies by measuring tumor volume with time.

Photodynamic therapy + thiotepa slowed tumor growth no better than PDT alone. At four weeks, tumors treated with PDT + Adriamycin were ~60% smaller than those treated with PDT alone. PDT alone slowed tumor growth better than either thiotepa or adriamycin alone (about 30 %). PDT alone and Mitomycin C alone were equivalent. The combination therapy with mitomycin C and BCG also slowed growth by ~60%. The researchers treated separate saline control and PDT alone groups for each drug group. Retardation of tumor growth by PDT alone was variable at 4 weeks. For the four groups of 10 mice treated with PDT alone, average tumor volume at the end of study was 3000, 2400, 1900 and 2400 mm^3. In fact PDT alone was no better than control in the BCG group. This variability makes these results difficult to interpret, nevertheless PDT + drug was superior to PDT alone or drug alone in three of four experiments. None of the therapies cured any mice. The following graphs present the results of this study.

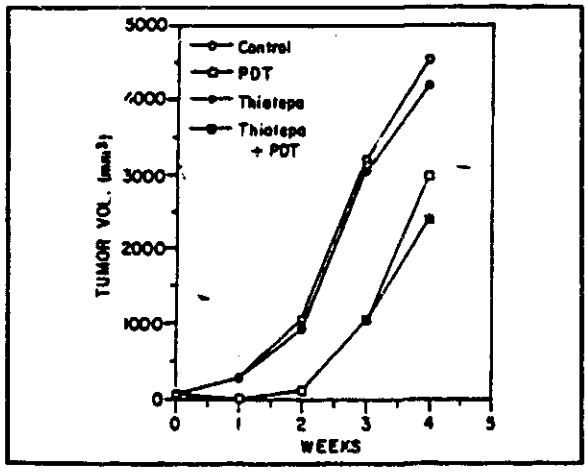


Figure 1. Effect on MBT-tumor of PDT or thiotepa (TT) alone or in combination.

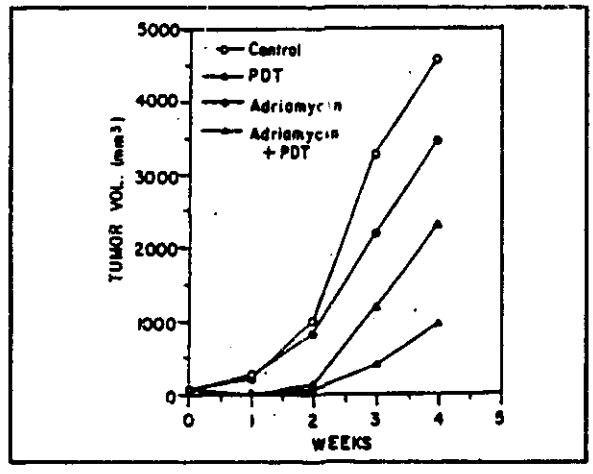


Figure 2. Effect on MBT-2 tumor of PDT or adriamycin (ADM) alone or in combination.

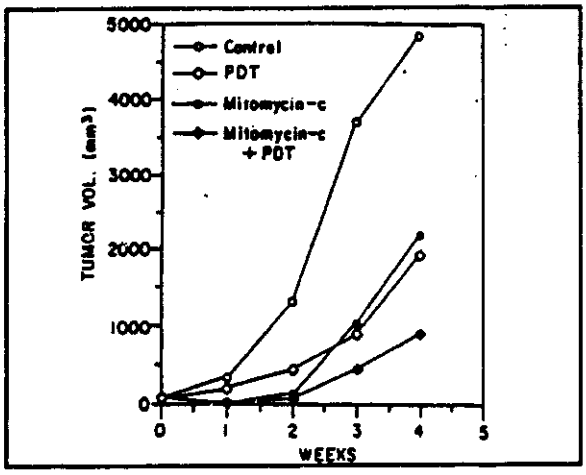


Figure 3. Effect on MBT-2 tumor of PDT or mitomycin-C (MMC) alone or in combination.

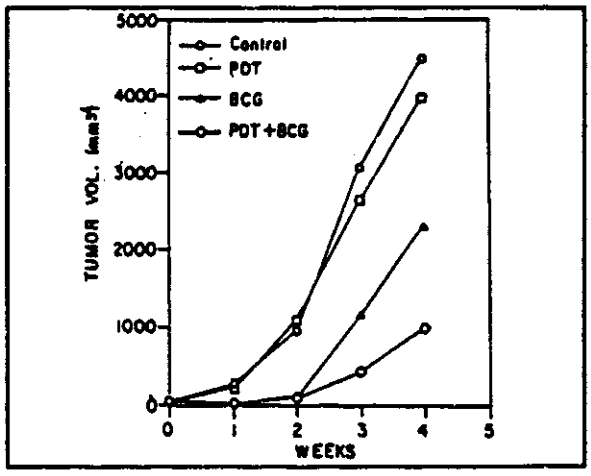


Figure 4. Effect on MBT-2 tumor of PDT or BCG alone or in combination.

67) Cowled PA and Forbes IJ. Photocytotoxicity *in vivo* of haematoporphyrin derivative components. Cancer Letters. 1985; **28**:107-114.

Cowled and Forbes transplanted lewis lung carcinoma cells to C57BL mice s.c. They treated these mice with HPD, hematoporphyrin, protoporphyrin or one of the three fractions of HPD separated by aqueous gel filtration, Photofrin, HPD aggregate, or HPD non-aggregate. These fractions are named in order of elution, thus in order of decreasing molecular size. Cowled and Forbes then irradiated the tumors with white light 24 hours post injection. The researchers evaluated tumor response as the time required for tumor regrowth in half the animals in a treatment group, TC_{50} in days. Fluorescence in tumor frozen sections demonstrates porphyrin uptake. They evaluated skin photosensitivity by measuring % increase in footpad thickness after irradiation. The following table presents the results of these experiments.

Porphyrin	TC_{50}	% increase footpad thickness	sd	tumor fluorescence
HPD	5	79	21	Positive
HPD Aggregate	5	69	9.9	Positive
HPD Non-Aggregate	0	0.8	6.7	Weak Positive
Hematoporphyrin	0	0	2	Negative
Protoporphyrin	0	-0.2	3	Negative
Photofrin	6	55.4	11.5	Positive

Dougherty *et al* (238) used reverse phase HPLC to determined that the major components of HPD are un-reacted hematoporphyrin (HP, 42 %) and hydroxyethylvinyldeuteroporphyrin (HDV, 34 %). When HPD is separated by gel filtration (exclusion 20,000) three major band appear. Photofrin

elutes first and is a mixture of covalently bound oligomers (ester and ether links between rings). The second band is HPD aggregate, non-covalently bound monomers of HP and HDV. The third band is non-aggregated monomers.

The table shows that HPD, HPD aggregate, and Photofrin all increase the TC_{50} and cause skin photosensitivity. The three porphyrin monomers, protoporphyrin, hematoporphyrin and HPD non-aggregate cause no slowing of tumor growth or skin photosensitivity. These monomers are all fluorescent, yet tumor does not fluoresce after mice receive these chemicals. This implies that these polar porphyrin monomers are not taken up by tumor.

68) Cowled PA *et al.* Potentiation of photodynamic therapy with haematoporphyrin derivatives by glucocorticoids. *Cancer Letters* 1985; **29**: 107-114.

Cowled et al gave glucocorticoids i.p. to mice with implanted Lewis lung carcinoma after they treated the tumors with PDT. Half the tumors in control mice receiving only PDT grew back in about 3.5 days, i.e. TC_{50} Methylprednisolone acetate, 0.6 mg/kg 24 and 28 hr post PDT, increased the TC_{50} to 8.3. Increasing the dose to 3.0 mg/kg did not significantly increase this effect. Hydrocortisone sodium succinate caused similar increases at 3.0 and 15 mg/kg. Methylprednisolone sodium succinate, 0.60 mg/kg, increased the TC_{50} to about 4.5. Increasing this dose to 3.0 mg/kg increased the TC_{50} to more than 8. Methylprednisolone acetate, 3.0 mg/kg -24 and 0 hr, given prophylactically decreased the TC_{50} to 1 day, profoundly decreasing the efficacy of HPD-PDT. The following graphs show some of these results.

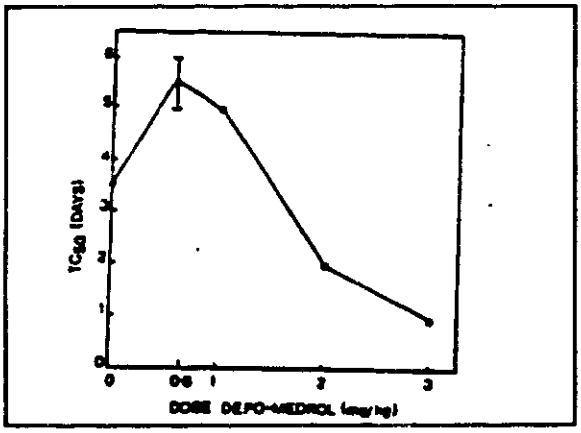


Figure 2. Relationship between dose of methylprednisolone acetate and TC_{50}. Mice with Lewis lung carcinoma were given HPD, 30 mg/kg plus methylprednisolone acetate i.p. twenty four hours later, a further dose of methylprednisolone acetate was given and the tumor treated with 200 a light.

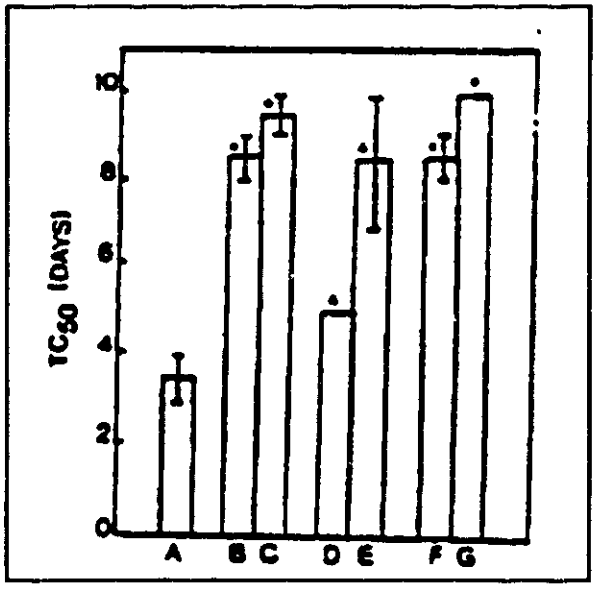


Figure 3. Administration of glucocorticoids after PDT. Mice with Lewis lung carcinoma were given HPD, 30 mg/kg followed 24 h later by 200 a irradiation to tumors. Glucocorticoids were adminis-tered i.p. 24 h and 48 h after treatment. (A) No glucocorticoid; (B) methylprednisolone acetate, 0.6 mg/kg; (C) methylprednisolone acetate, 3.0 mg/kg; (D) methylprednisolone sodium succinate, 0.6 mg/kg; (E) methylprednisolone sodium succinate, 3.0 mg/kg; (F) hydrocortisone sodium succinate, 3.0 mg/kg; (G) hydrocortisone sodium succinate, 15.0 mg/kg. • , $p < 0.05$. , $p < 0.01$, , $p < 0.001$.

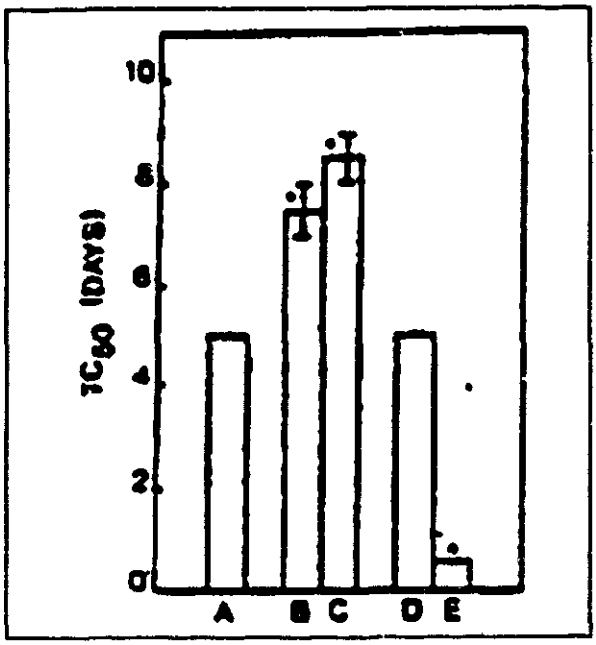


Figure 4. Interaction between glucocorticoids and PDT of B16 melanoma. Mice with B16 melanoma were given HPD, 30 mg/kg, followed 24 h later by 100 a light to tumors. (A) No glucocorticoids; (B) hydrocortisone sodium succinate, 3.0 mg/kg administered 24 h and 48 h post PDT; (C) hydrocortisone sodium succinate, 15.0 mg/kg administered 24 h and 48 h post PDT; (D) hydrocortisone sodium succinate, 15.0 mg/kg administered with HPD and at time of irradiation; (E) methylprednisolone acetate, 3.0 mg/kg administered with HPD and at time of irradiation. , $p < 0.01$, , $p < 0.001$.

When these researchers gave methylprednisolone acetate concurrently with HPD intra-tumor fluorescence decreased. This implies that glucocorticoids directly effect HPD uptake. Glucocorticoids did not decrease skin photosensitivity.

The decrease in efficacy when glucocorticoids are given prophylactically may result from a decrease in capillary permeability in the tumor. Glucocorticoids also may decrease phagocytosis, this process is responsible for at least some HPD uptake. Glucocorticoids stab-ilize lysosomal membranes. Much of the cell damage cause by PDT results from the rupture of lysosomal membranes.

The increase in efficacy when glucocorticoids are given after PDT are harder to explain. These drugs may decrease the local immune response to PDT damage and slow tissue repair. That glucocorticoids decrease tumor fluorescence suggests that porphyrin monomer uptake is diminished. These monomers prob-ably enter by phagocytosis. Porphyrin oligomers or aggregates are much less fluorescent than monomers. These compounds probably enter the cell by a process that does not involve phagocytosis, see ref 87. This research does not provide any evidence about the intracellular concentration of these compounds.

72) Okunaka T *et al.* A comparison between argon-dye and excimer-dye laser for photodynamic effect in transplanted mouse tumor. *Jpn J Cancer Res.* 1992; 83:226-231.

Okunaka *et al* compared the depth of necrosis caused by PDT with two different laser sources. The laser used in most PDT is an argon dye laser. They found that an excimer-dye laser, which pulses laser light, caused deeper tumor necrosis at equal energies. The tumor model was mouse kidney sarcoma implanted in BALB/c mice. The following table presents the results of this study.

Laser	irradiation	Energy density J/cm^2	Depth of necrosis mm	sd
Argon-dye	200 mW	50	4.1	0.8
Argon-dye	200 mW	200	9.4	1.2
Excimer-dye	6 mJ/pulseX30 Hz	50	14.0	1.6

Laser light without HPD, control, caused no necrosis. The authors state the excimer laser PDT caused no thermal changes in tumor tissue. The depth of tumor necrosis decreased with decreasing pulse energy, pulse frequency and energy density. The authors explanation of this result is implausible. They argue that the peak energy of the excimer laser is higher during a pulse, however the energy of a 630 nm photon is constant regardless of its source. The energy density is the same for both lasers at 50 J/cm^2 so the same number of photons are hitting the tumor over a given time. The authors argue that the lifetime of trip-let HPD is greater than the pulse frequency. The 690 nm phosphorescence decays with a lifetime ($t_{1/e}$) of $8\pm2\ X10^{-3}$ sec. This lifetime is a third the 33 msec between pulses. The authors speculate that the increased penetration may be related to saturation of the porphyrin excited state near the surface of the tumor. This explanation may be plausible. This study suggests that PDT with excimer laser irradiation may be more ef-fective than PDT with argon dye irradiation. The mechanism for this increased effectiveness is unexplained.

77) Nelson JS *et al.* Use of multiple photosensitizers and wavelengths during photodynamic therapy: a new approach to enhance tumor eradication. *J National Cancer Inst.* 1990; 82:868-873.

Nelson *et al* gave varying doses of Photofrin and meso-tetra-(4-sulfonatophenyl)-porphyrin ($TPPS_4$) to mice bearing EMT-6 mammary tumors. They gave groups of 10 mice either 5 mg/kg of Photofrin or 5 mg/kg of $TPPS_4$ or 2.5 mg/kg of each drug i.v. 24 hr before PDT. They irradiated the tumors with varying energy densities of 630 nm light alone (Photofrin groups), 658 nm light alone ($TPPS_4$ groups), or both (groups receiving both drugs). Tumor response was synergistic. More tumors responded to the Photofrin plus $TPPS_4$ treatment than to either drug alone. $TPPS_4$ alone was more effective than Photofrin alone in all five experiments. The table below shows tumor response to these different treatments. The authors argue that lower doses of two photosensitizing porphyrins may be safer than a larger dose of a single compound. Lower initial doses could be cleared more rapidly if the clearance mechanisms are different. $TPPS_4$ should be cleared faster than Photofrin.

Group	Energy density J/cm^2		Drug dose mg/kg		Complete response	Partial response	No Response	Percent cured
	630 nm	658 nm	Photofrin	TPPS4				
1	80		5.0		10			100%
		80		5.0	10			100%
	40	40	2.5	2.5	10			100%
2	60		5.0		5	5		50%
		60		5.0	6	4		60%
	30	30	2.5	2.5	10			100%
3	40		5.0		2	5	3	20%
		40		5.0	3	7		30%
	20	20	2.5	2.5	7	3		70%
4	20		5.0			3	7	0%
		20		5.0		5	5	0%
	10	10	2.5	2.5	3	7		30%
5	10		5.0				10	0%
		10		5.0			10	0%
	5	5	2.5	2.5		2	8	0%

81) Nelson JS *et al*. Glucose administration combined with photodynamic therapy of cancer improves therapeutic efficacy. Lasers Surg Med. 1992; 12:153-158.

Nelson *et al* studied the change in tumor response to PDT associated with administration of glucose (as 50 % dextrose injection, USP). They gave mice baring C3HBA mammary adenocarcinoma 3.0 g/kg glucose 1 hr prior and at 1, 3, 5, 7, 9, 11, and 16 hours after they injected Photofrin, 10 mg/kg. The laser light was 630 nm 100 mW/cm^2. Immediately after PDT, the researchers gave the mice 6 g/kg glucose i.p. The following table shows tumor response as a function of glucose dose and energy density.

Energy densit, J/cm^2	Glucose	Complete response	Partial response	No response	Percent cured
450	-	10			100%
	+	10			100%
400	-	8	2		80%
	+	10			100%
350	-	6	4		60%
	+	10			100%
300	-	5	5		50%
	+	10			100%
250	-	5	5		50%
	+	7	3		70%
200	-	3	7		30%
	+	5	5		50%
150	-	1	7	2	10%
	+	3	7		30%
100	-		7	3	0%
	+	1	9		10%
50	-		2	8	0%
	+		10		0%

The authors defined cure as no palpable mass four weeks post PDT. The investigators provide no statistical analysis of this data, but the increased tumor response with glucose is clear. Only groups receiving PDT+glucose achieved 100% cure. Controls all progressed rapidly. Other researchers have noted that hyperglycemia causes the pH of solid tumors to increase. The authors postulate that pH trapping of protonated Photofrin increases intratumor concentration. Hyperglycemia also decreases tumor perfusion. Decreased blood flow increases the efficacy of PDT if it is initiated after the formation of singlet oxygen. Nevertheless, the authors also knew that high glucose concentrations would decrease intratumor O_2 concentration, and that O_2 was necessary for effective PDT, ref 16. Thus, they allowed 32 hours between the last 3 g/kg dose of glucose and PDT. The dosing procedure they choose loaded tumor with Photofrin, then allowed reoxygenation. The final large dose of glucose after PDT decreased tumor perfusion after radical formation. These factors combined to increase the efficacy of PDT.

87) Roberts WG and Berns MW. In vitro Photosensitization I. Cellular uptake and subcellular localization of mono-L-aspartyl chlorin 36, chloro-aluminum sulfonated phthalocyanine and Photofrin II. *Lasers Surg Med.* 1989; 9:90-101.

Inhibition of pinocytosis decreases the uptake mono-L-aspartyl chlorin 36 (MACE) and chloro-aluminum sulfonated phthalocyanine (CASPc), but not Photofrin into CHO cells. This research suggests that Photofrin enters cells by diffusion across the membrane. Photofrin associates strongly with membranous organelle, especially mitochondria.

95) Ma LW *et al.* Effect of mitomycin C on the uptake of Photofrin II in human colon adenocarcinoma cell line. *Cancer Letters.* 1992; 64:155-162.

Mitomycin C (MC) retards cells in G_2/M phase at in vitro concentrations of 0.10 µg/ml. Cell surface area increases during these phases 1.3 to 2.7 fold. Ma *et al.* added 10 µg/ml Photofrin to WiDr adeno-carcinoma cells 24 hours after they retarded cell division with MC. They measured Photofrin

uptake by flow cytometric fluoroscopy. Photofrin uptake increased linearly with cell surface area. This result supports the finding of reference # 87. Photofrin appears to enter cells by diffusion across the membrane. The following graph shows the results of this research.

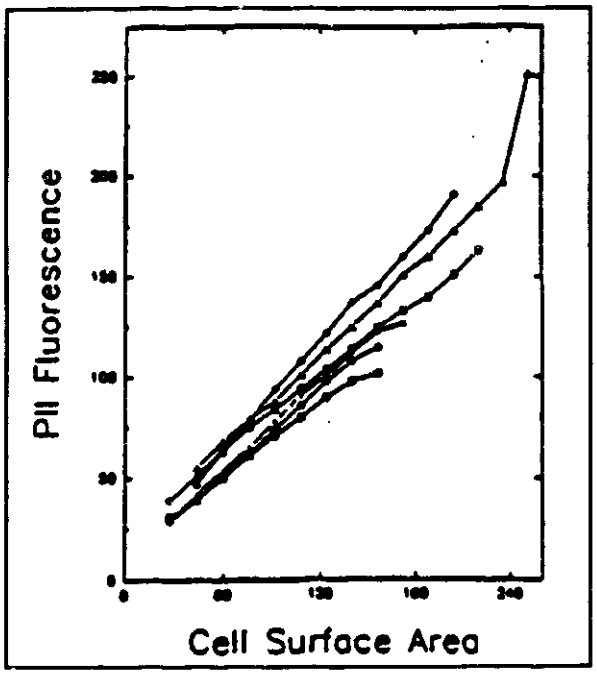


Figure 5. Cellular Photofrin fluorescence as a function of cell surface area (LSI). Symbols: control cells incubated with Photofrin for 16 h; ✱ cells were exposed to MC for 2 hours, washed and incubated further in pure medium with 10% FCS for 22 h and the Photofrin was given for 16 h; 9 cell exposed to MC for 4 hours, washed and incubated in pure medium with 10% FCS for 20 hours and the Photofrin was added for 16 hours; ▲ 8 hours, MC, washing and 16 h, pure medium with 10% FCS and then Photofrin 16 hours; ♦ 4 hours, MC, washing and 44 hours pure medium with 10% FCS, followed by Photofrin 16 hours; 4 hours, MC, washing and 68 hours, pure medium with 10% FCS and then Photofrin 16 hours. Each point represents approximately 500-1000 cells. MC concentrations = 0.1μg/ml. Photofrin concentration = 10 μg/ml.

98) Gonzalez S *et al.* Treatment of Dunning R3327-AT rat prostate tumors with photodynamic therapy in combination with misonidazole. *Cancer Res.* 1986; 46:2858-2862.

Misonidazole (MISO) is a hypoxic cell radio-sensitizer. Hypoxia decreases the cytotoxicity of Photofrin PDT. Gonzalez *et al* treated rats baring R3327-AT prostate tumors with MISO, 0.5 mg/ml. Thirty minutes later these researchers gave the rats 15 mg/kg of Photofrin or 20 mg/kg HPD. They irradiated the tumors four hours later with 630 nm laser light. They measured tumor response as time to regrow to 10X treatment volume. Hyperthermia increases the effectiveness of PDT, so the researchers tested the therapy at 40-41 and 44-45 C. The table below presents the results of this study.

Treatment Group	N	Photosensitizer	Light dose J	MISO mg/g	Growth delay days	Significance
Control	10		1224		0.0	
Laser dose 1	9	HPD	2376		3.1	<0.01
Laser dose 2	9	HPD	2160		8.1	<0.01
Laser only 44-45 C	5		2160		0.5	NS
PDT 40-41 C	10	Photofrin	2160		8.8	<0.01
PDT 44-45 C	5	Photofrin	2160		13.3	<0.01
MISO + PDT 40-41 C	10	Photofrin	2160	0.5 before	15.2	<0.01
MISO + PDT 44-45 C	5	Photofrin	2160	0.5 before	15.0	<0.01
PDT + MISO 40-41 C	10	Photofrin	2160	0.5 after	16.3	<0.01
MISO	10		2160	0.5 before	0.2	NS
MISO + Laser 40-41 C	10		2160	0.5 before	2.2	<0.01
MISO + Laser 44-45 C	8		2160	0.5 before	4.4	<0.0

On average MISO pre-treatment with PDT delayed tumor growth almost twice as long as PDT alone at 40-41 C. The effect of MISO pretreatment was less pronounced at 44-45 C. When the researchers gave MISO 30 minutes after PDT tumor growth was delayed over twice as long as with PDT alone. Twenty percent of rats treated with MISO before PDT and 70% treated with MISO after PDT achieved cures (local control at 33 days). Adding MISO to cells before or after PDT in the presence of photofrin causes an increase in growth delay. This increase is synergistic but small (38% increase over additive effect when MISO was added before, 48% when MISO was added after). The growth delay caused by MISO is about the same as that caused by increased temperatures. At higher temperatures the synergy vanishes.

Growth delay does not increase beyond about 16 days. One of the mechanisms of MISO radio-sensitization is thiol depletion (EJ Hall, 1992, *Radiat. Res.* 129:235). Thiols scavenge the destructive radicals created by PDT. Damage increases as PDT generated radicals consume thiols. This could account for the observed synergy. Nevertheless, the tumor growth cannot be delayed beyond the limit of maximal thiol depletion.

99) Santus R *et al.* Protection against light-activated Photofrin II killing of tumor cells by nitroimidazoles. *Radiat Res.* 1992; 130:31-37.

Nitroimidazoles quench the porphyrin triplet state. Thus these chemicals should prevent the forma-tion of singlet oxygen. Santus et al treated EMT-6 cells in vitro with Photofrin, 5 μg/ml overnight. Then they added etanidazole (ETAN), MISO or trifluoromisonidazole (TF-MISO). One hour later they irradiated the cells with 630 nm laser light. The following graph demonstrates the protection against PDT cytotoxicity caused by these drugs.

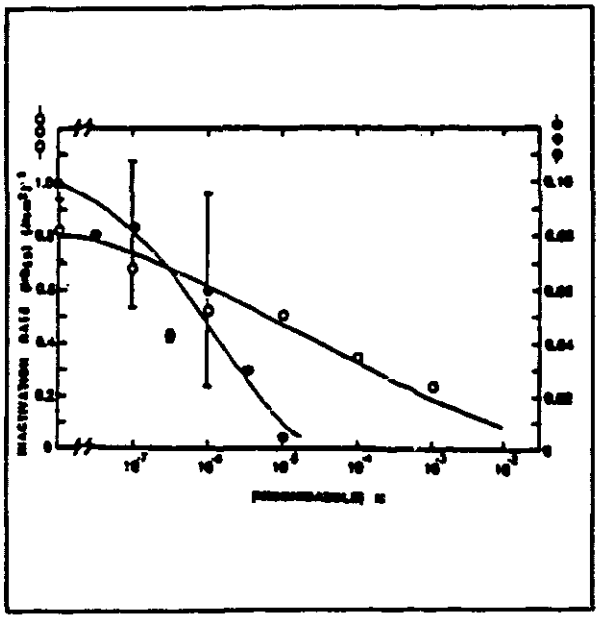


Figure 3. The effect of various concentrations of misonidazole on the photo-inactivation rate of EMT-6 tumor cells (reciprocal of light dose required to kill 50% of cell population) equilibrated with 0.3% O_2 in the gase phase after short-term ( ) and long-term ( ) exposures to Photofrin.

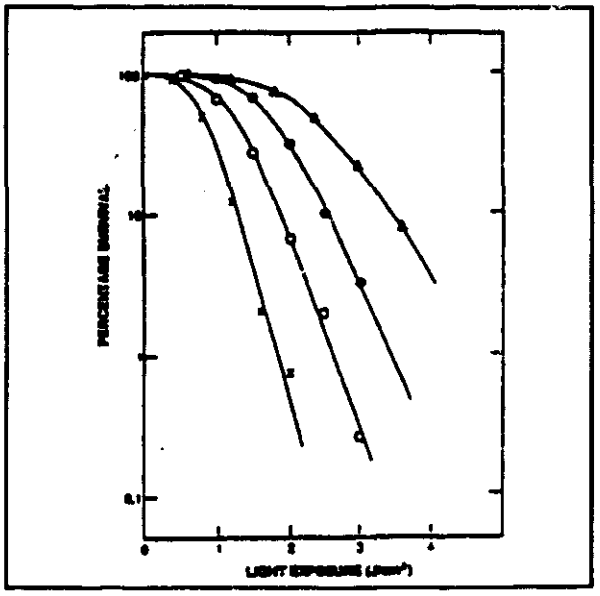


Figure 4. The inactivation of aerobic EMT-6 tumor cells after various doses of 630 nm light in the absence (✱) and presence of 5 mM etanidazole ( ), misonidazole ( ) and trifluoromisonidazole (□) after long-term exposure to Photofrin.

The nitroimidazoles afforded little protection when cells were incubated with Photofrin for only one hour. When the researchers increased the O_2concentration in the air above the cells the protection against PDT cytotoxicity increased. These results are not necessarily in disagreement with reference 98. The cells killed by MISO in solid tumors in vivo were probably beyond the penetration of the laser light. The O_2tension in cells killed by PDT was probably low enough that nitroimidazole quenching was less effective. In vivo, the thiol scavenging mechanism of nitroimidazoles probably predominated.

101) Foultier M-T *et al.* Photodynamic treatment of normal endothelial cells or glioma cells in vitro. *Surg Neurol.* 1992; 37:83-88.

When these researchers added exogenous prostaglandin to endothelial cells or C6 cells, PDT killed a higher fraction of the cells. Indomethacin, an inhibitor of prostaglandin synthesis, added to the cells before PDT protected the cells, increasing survival from 55%, control, to 85 %.

102) Ben-Hur E, *et al.* Protection by the fluoride ion against phthalocyanine-induced photodynamic killing of Chinese hamster cells. *Photochem Photobiol.* 1992: 55:231-237.

Ben-Hur *et al.* incubated Chinese hamster V79 lung fibroblasts with phthalocyanine and Fluoride ion prior to PDT. Fluoride ion protected the cells from PDT, increasing the survival from 2%, controls, to 50% at 18 kJ/m^2. Added fluoride had no effect on PDT when the investigators used Photofrin as the photosensitizer.

104) Purkiss SF *et al.* In vitro modulation of heamatoporphyrin derivative photodynamic therapy on colorectal carcinoma multicellular spheroids by verapamil. *Br J Surg* 1992; 79: 120-125.

Purkiss *et al.* incubated HRT18 and HT29 human colorectal multicellular tumor spheroids (MTS) with HPD and verapamil at different concentrations. This HPD was not supplied by the sponsor, these investigators synthesized their own. They irradiated the MTS cultures with white light, tungsten, at 4 J/cm^2. Verapamil reduced the volume growth of HRT18 MTS cultures proportional to concentration between 1 and 4 µM. Verapamil at 4 µM decreased MTS volume growth by > 50% over control at eight days. The control contained no verapamil, HPD 1 µg/ml. These concentrations of verapamil were even more effective at inhibiting the regrowth of HT29 MTS cultures. One µg/ml verapamil reduced the relative volume growth to one third of controls on day 10. Increased verapamil concentrations decreased survival only slightly more, suggesting that above 1 µg/ml the mechanism for this increased PDT efficacy is saturated. The following graph shows these results.

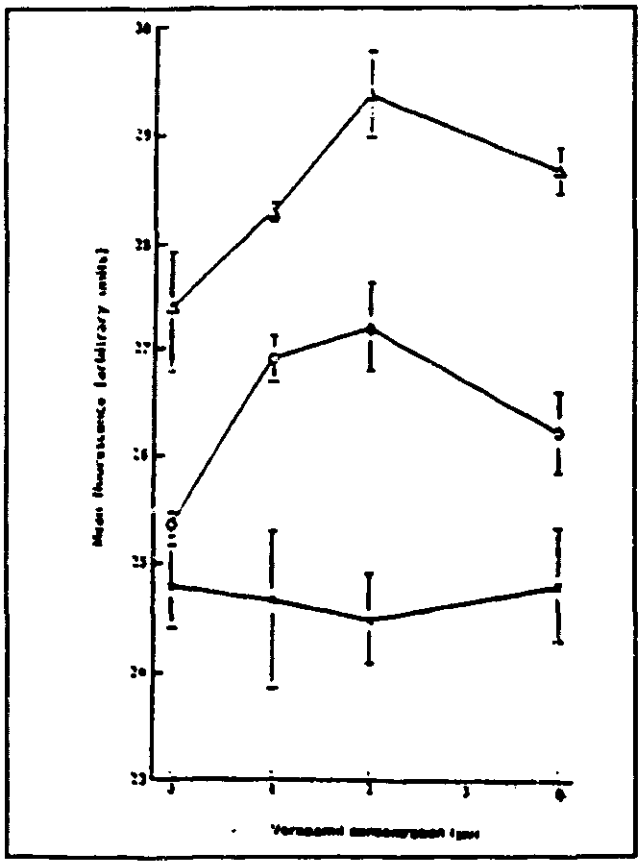


Figure 7. The effects of verapamil on the relative HPD fluorescence of single cells derived from disaggregated HRT18 spheroids measured by flow cytometry. HRT18 spheroids were incubated for 24 hours in the presence or absence of HPD (0, 1 and 2 µg/ml and with or without verapamil (0, 1, 2 and 4 µM). Values are means (s.e.m.) of the relative fluoescence in arbitrary units of cells from five separate experiments. —— HPD 0 µg/ml; —○— HPD 1 µg/ml; —□— HPD 2 µg/ml.

These investigators also measured the efflux of HPD into the culture medium after incubation and washing. The concentration of HPD in the medium 24 hr after MTS cultures were preincubated with HPD and verapamil was 18.1 ± 2.8 units/ml. The concentration of HPD in the medium of control cultures, no verapamil, was 93.2 ± 18.8 units/ml. Thus, verapamil decreases the efflux of HPD from tumor cells by > 80 %. Flow cytometric fluorescence measurements showed that the concentration of HPD inside cells increased with the concentration of verapamil in the preincubation media.

These findings are quite interesting. The authors postulate that verapamil inhibits HPD efflux through its inhibition of p-glycoprotein. P-glycoprotein is usually responsible excluding large lipophilic cations such as doxirubicin from cancer cells. HPD would be an unusual substrate for the as yet ill-defined mechanism of p-glycoprotein.

108) Boyle D and Potter W. Photo-bleaching of Photofrin II as a means of elimination skin photosensitivity. *Photochem Photobiol.* 1987; 46:997-1001.

Boyle and Potter gave mice 5 mg/kg Photofrin. Twenty-four hours later they irradiated the left foot of one group with low intensity light, 18 J/cm^2. They repeated this light treatment each day through day 6. On day 7, they irradiated both the right and left foot of the mice with 135 J/cm^2. This treatment severely damaged the right foot of these mice, i.e. the foot with no pre-treatment. Nevertheless, intense irradiation did not damage the pre-treated left foot. Damage to the right foot of these mice was similar to damage to irradiated control animals, with Photofrin.

These experiments show that Photofrin adsorbed by the skin is eliminated by photo-bleaching. This suggests that patients receiving Photofrin should expose themselves to low levels of indoor white light during the weeks following the therapy. Such low level exposure probably serves to decrease Photofrin photosensitivity more rapidly than if the patient stays in complete darkness.

122) Hunt DWC *et al.* Photofrin, but not benzoporphyrin derivative, stimulates hematopoiesis in the mouse. *Immunopharmacology.* 1993; 26:203-212.

Hunt *et al* gave DBA-2 mice Photofrin, 10 and 25 mg/kg. Twenty-four hours later they harvested spleens and bone marrow. They plated cells from these organs and compared the number of colony forming units-granulocyte-macrophage (CFU-GM) with controls after 7 days. The table below shows that the spleens of mice treated with Photofrin i.p. weighed more than spleens from controls. Spleens from mice treated with Photofrin i.v. weighed more, but the difference did not reach significance. Nevertheless, the relative number of cells was significantly greater for both routes of administration.

			Spleen Parameter						
Treatment	Dose	Route	n	relative weight	sd	Total Cells	sd	Relative cell number	sd
Solvent	0	i.v.	4	0.33	0.06	4.43	0.12	1.98	0.12
BPD	10	i.v.	4	0.40	0.05	4.75	1.12	2.28	0.35
Solvent	0	i.v.	4	0.42	0.03	5.25	0.44	2.17	0.18
Photofrin	10	i.v.	4	0.47	0.04	7.56*	0.70	3.03*	0.29
Photofrin	25	i.v.	5	0.50	0.05	7.41*	0.47	3.07*	0.2
Solvent	0	i.p.	47	0.37	0.01	4.70	0.15	2.09	0.07
Photofrin	10	i.p.	9	0.53*	0.05	6.86*	0.67	2.93*	0.25
Photofrin	25	i.p.	29	0.58*	0.03	7.87*	0.80	3.39*	0.35

* $p<0.05$

Photofrin caused significant increases in the CFU-GM in both bone marrow and spleen. Stimulation was maximal at 72 hr post dosing then declined toward normal. The following graph presents these results.

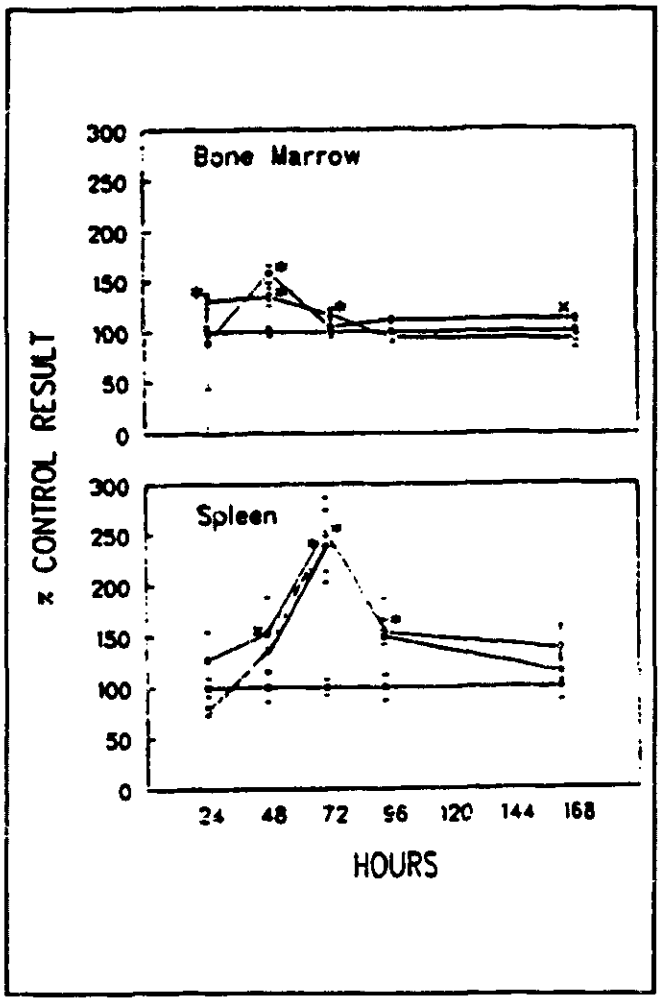


Figure 2: Relative frequencies of CFU-GM in BM an spleens of normal mice injected i.p. with 5% dextrose ([illegible]) *presented as the mean percentage (%) ± the standard error (SE) of the results obtained for solvent-injected mice sampled in parallel. Each data point represents the result for 6-16 mice. Mean number of colonies/plate for control mice ranged from 136-146 (BM) and 70-95 (spleen). Few (0-2) colonies were formed in the absence of spleen conditioned media.*

x p < 0 05 * p < 0 005

Photofrin also increased the total white cell count and the lymphocyte count about 38% at seven days post dosing. Increases in neutrophils, monocytes and eosinophiles did not reach significance. The authors speculate that this immune stimulation is secondary to Photofrin mediated release of cytokines. The immune system may simply be responding to large foreign molecules bound to cell membranes.

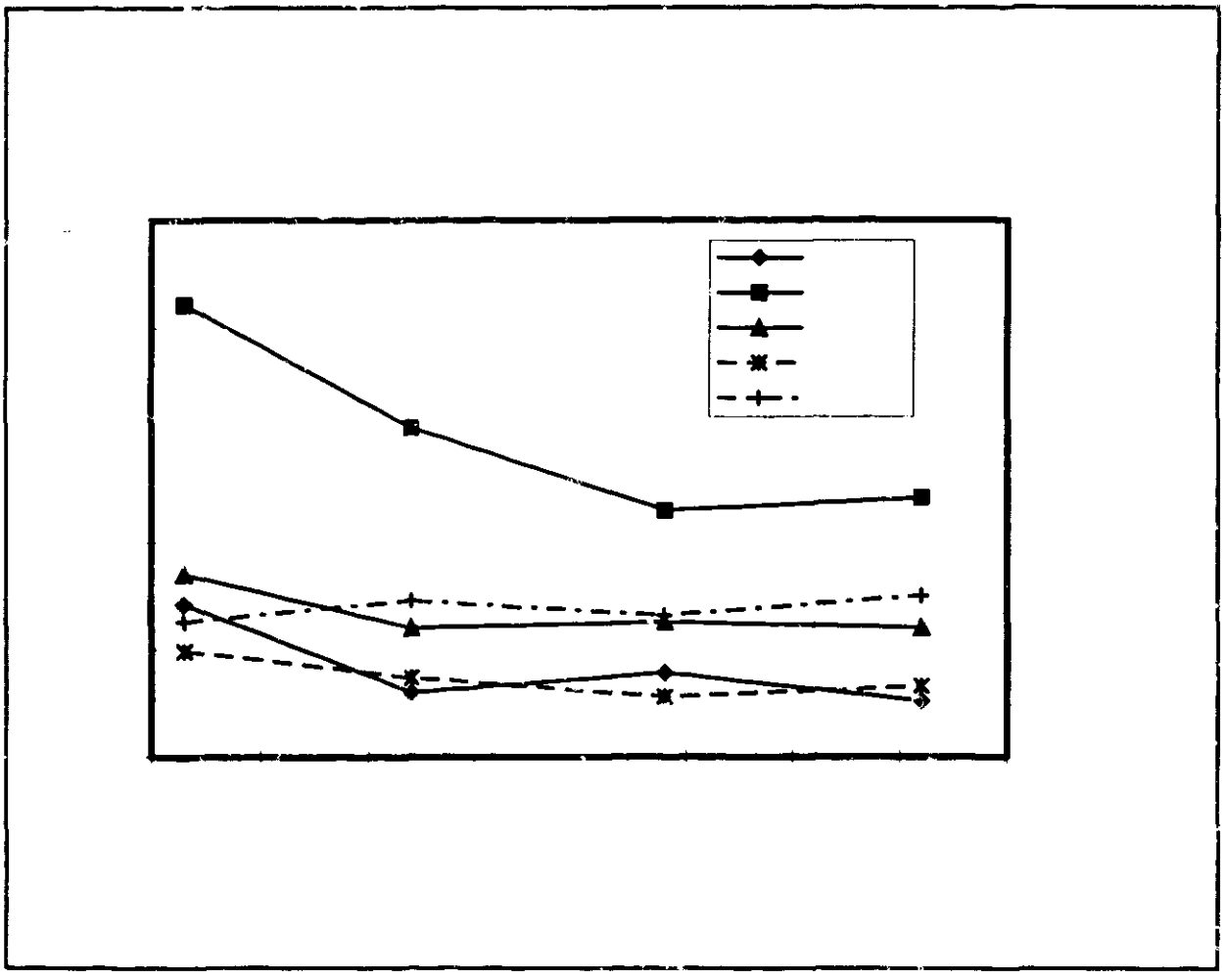
225) Perry RR *et al.* Intravenous vs intraperitoneal sensitizer: Implications for intraperitoneal photodynamic therapy. *Photochem Photobiol.* 1991;53(3):335-340.

Perry *et al.* gave Photofrin, 10 mg/kg, i.v. via tail vein or i.p. to normal mice or mice bearing implanted 3-Methylcholanthrene induced tumors. They killed the mice at 3, 24, 48, and 72 hr post injection. They then determined Photofrin concentration in tumors and tissues by the fluorescence of acidic methanol extracts. Again, as the following table shows, they found the highest concentrations of Photofrin in the liver. Much of the Photofrin remained even after 72 hours. Like Pantelides *et al.* (ref 207) these researchers observed that the maximum concentrations of Photofrin in the liver were twice as

high when they gave it i.v. as when they gave it i.p.

Sensitizer concentration in tumor and normal tissue after i.p. and i.v. injection.

Time		Tumor	s.d.	Liver	s.d.	Stom.	s.d.	Small Bowel	s.d.	Large Bowel	s.d.	Kid.	s.d.	Panc.	s.d.
hr															
3	i.p.	49	11	63	11	38	6	39	8	33	3	36	5	27	5
	i.v.	71	19	211	29	34	4	30	2	40	7	85	9	31	9
24	i.p.	37	6	73	12	25	2	23	3	30	3	44	8	24	3
	i.v.	30	2	154	11	25	2	25	2	34	3	60	4	14	2
48	i.p.	28	7	65	11	30	5	21	2	38	5	41	7	24	3
	i.v.	39	12	115	7	34	4	28	2	35	3	63	3	19	3
72	i.p.	33	5	75	10	33	3	20	2	41	5	37	4	28	3
	i.v.	26	0	121	9	35	3	24	1	41	5	60	5	18	2



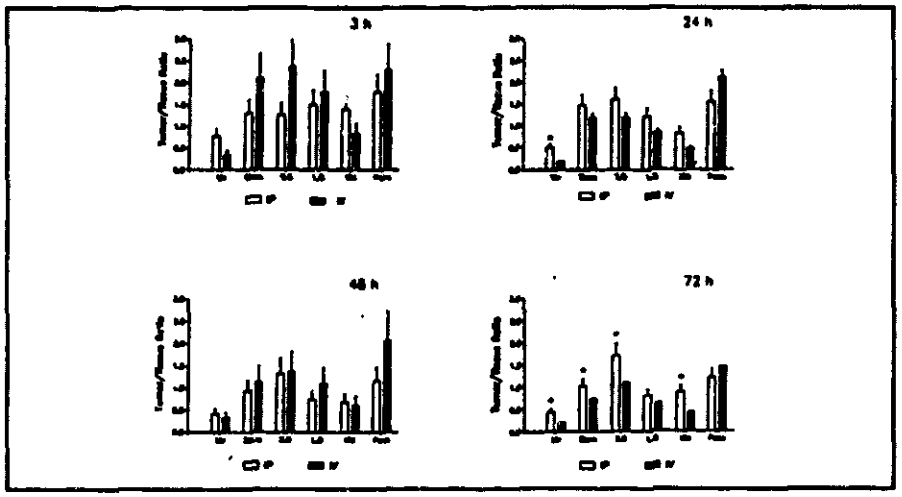


Figure 2. Tumor to norm tissue sensitizer ratios when 10 mg/kg Photofrin II is administered i.v. or i.p. Tissues tested: Liv = liver, Stom = stomach, S.B. = small bowel; L.B. = large bowel; Kid = kidney; Panc = pancreas. At three hours, tumor/tissue ratios appear more favorable after i.v. injection with the exception of the liver and kidney although these differences are not statistically significant. After three hours there appears to be a trend of higher tumor to normal tissue ratios in the i.p. group which is most apparent 72 hours after sensitizer administration (* $p < 0.05$, i.p. compared to i.v.).

The authors did not do ANOVA on these data so their statistical analysis is inappropriate. The graph shows that the concentration of Photofrin in this particular tumor is similar to that in the other organs tested. The ratio of Photofrin in tumor to that in normal non-adjacent tissue did not vary significantly with the route of administration until 72 hours post dosing. At that time, the investigators observed that the ratio of $[\text{Photofrin}]_{\text{tumor}}$ to $[\text{Photofrin}]_{\text{normal tissue}}$ in liver, stomach, small bowl and kidney, was greater when they administered Photofrin i.p. than when they gave it i.v. This was the goal of this paper. Nevertheless, these improved ratios were one or less in all tissues but small bowel. Much of the Photofrin was not absorbed when given i.p. The Photofrin probably adsorbed to the peritoneal surfaces. This data again suggests that the ratio of $[\text{Photofrin}]_{\text{tumor}}$ to $[\text{Photofrin}]_{\text{normal tissue}}$ is tumor and tissue specific.

229) Fingar VH *et al.* The effects of thromboxane inhibitors on the microvasculature and tumor response to photodynamic therapy. *Photochem Photobiol.* 1993; 57:856-861.

Working on the knowledge that photodynamic therapy cause clotting and vessel constriction as an early sequelae, Finger *et al.* postulated that thromboxane inhibitors would diminish the damage from Photofrin PDT. They gave rats baring implanted chondrosarcoma Photofrin, 25 mg/kg. Just prior to PDT they gave R68070, a thromboxane synthetase inhibitor, SQ-29548, a thromboxane receptor agonist, or flunarizine, an inhibitor of platelet shape change. They measured vessel constriction and tumor response.

SQ-29548 decreased thromboxane concentrations by more than 50% below controls. Flunarizine and R68070 did not affect thromboxane concentrations. SQ-29548 and R68070 reduced vessel constriction and flunarizine prevented it. SQ-29548 and R68070 inhibited the PDT associated increase in vascular permeability, flunarizine did not. All three compounds markedly reduced tumor cures. These results suggest that the changes in vascular permeability and the aggregation of platelets caused by PDT are responsible for much of the tumor destruction. These compounds may also protect the tumor by some other more direct mechanism. The following graphs shows these results.

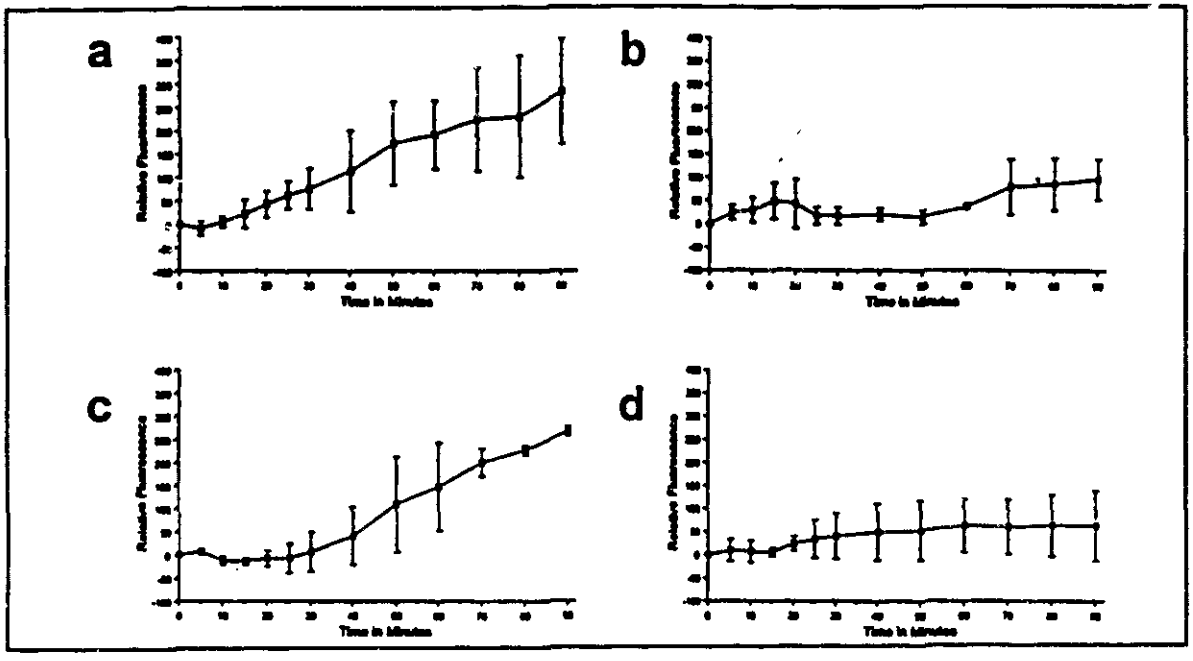


Figure 3. Alteration in venule permeability to fluorescein-labeled albumin. Animals were given Photofrin i.v. at a dose of 25 mg/kg, 24 hours before light treatment. The light treatment was 135 J/cm² 630 nm delivered during the first 30 min of the experiment. (a) Animals given no inhibitor. (b) Animals given 5 mg/kg R68070 1 hour before light treatment. (c) Animals given 50 mg/kg Flunarizine p.o., 2 hours before light treatment. (d) Animals given a continuous infusion of 10 µg/kg/min SQ-29584 after a loading dose of 0.1 mg/kg i.a., one hour before light treatment. Points represent the meansof relative fluorescence for three to six experiments. Bars represent 2 SME. Figure 3a is reprinted with permission from Cancer Research.

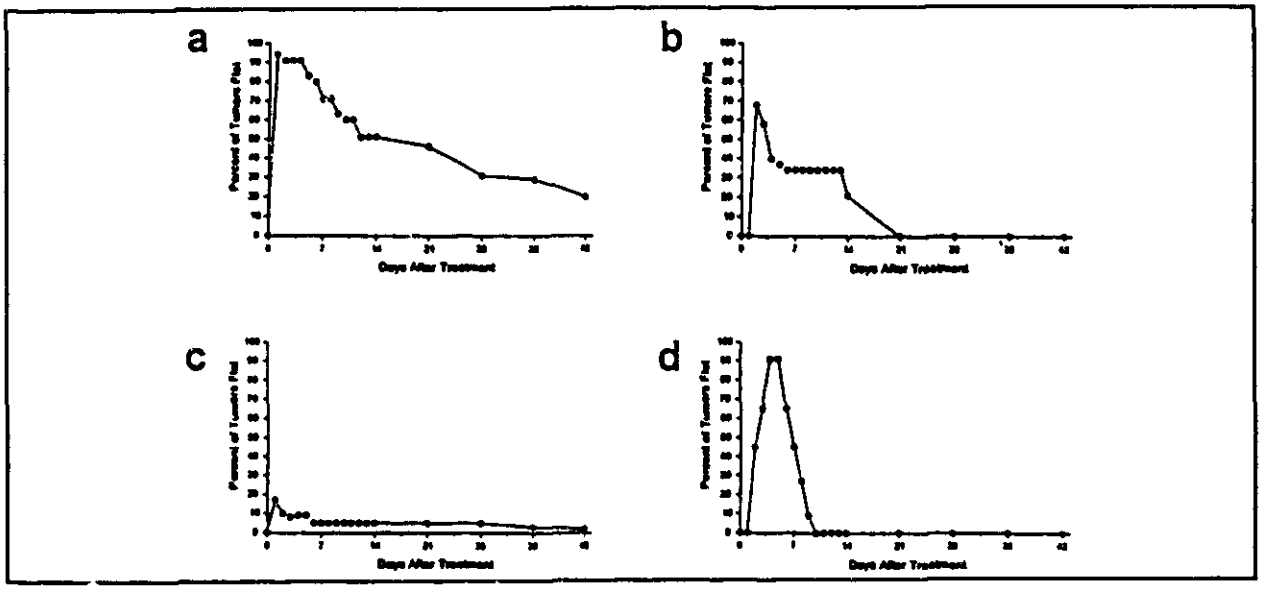


Figure 4. Tumor response to PDT. Animals were given Photofrin i.v. at a dose of 25 mg/kg, 24 hours before light treatment. The light treatment was 135 J/cm² 630 nm, delivered to a 2 cm diameter spot containing a tumor on the right hind limb of the animal. Tumor response was assessed daily for 14 days and weekly thereafter for a total of 42 days. (a) Animals given no inhibitor (n = 35). (b) Animals given 5 mg/kg R68070 one hour before the light treatment (n = 38). (c) Animals given 50 mg/kg Flunarizine p.o., two hours before the light treatment (n = 33). (d) Animals given a continuous infusions of 10 µg/kg/min SQ-29548 after a loading dose of 0.1 mg/kg i.a., one hour before the light treatment (n = 11).

230) Taber SW, *et al.* The effects of aspirin on microvasculature after photodynamic therapy. *Photochem Photobiol.* 1993;57:856-861.

Taber *et al.* gave aspirin to rats prior to Photofrin PDT. Aspirin inhibited venule leakage of albumin and reduced the increase in interstitial pressure after treatment. Nevertheless, aspirin did not reduce vessel constriction or tumor response. These results suggest that the increase in vessel permeability associated with Photofrin PDT does not contribute to the tumor response.

240) Everson JF, *et al.* Tumor-localizing and photosensitizing properties of the main component of Hematoporphyrin Derivative. *Cancer Res.* 1984, 44:482-486. QLT did not submit this article.

Everson *et al.* synthesized HPD by the method of Moan et al. (in D Kessel and TJ Dougherty eds. Porphyrin Photo-sensitization, p 165-179, Plenum Press, 1983). They labeled 200 mg of this synthesized HPD with tritium, 1.3 mCi/mg. Both the labeled and unlabeled HPD eluted from reverse phase HPLC with chromatograms identical to commercially available Photofrin. Judging by the date this has to be Photofrin synthetic scheme I, i.e. not purified by gel filtration. These researchers identified three major polar compon-ents in the synthesized Photofrin as unreacted hematoporphyrin (HP, component 2) and isomers of 2(4)-hydroxyethyl-4(2)-vinyl-deuteroporphyrin, HVD, component 4. The gel filtration step of synthetic scheme IR and II eliminates these monomeric porphyrins. They also account for most of the fluorescence of HPD. The authors pooled all the peaks that eluted after the HVD isomers as component 7. Component 7 was not significantly fluorescent, it contained the higher molecular weight oligomers, it was less polar than the other components, and the absorption maxima of the Soret peak was shifted to shorter wavelengths (<390 nm).

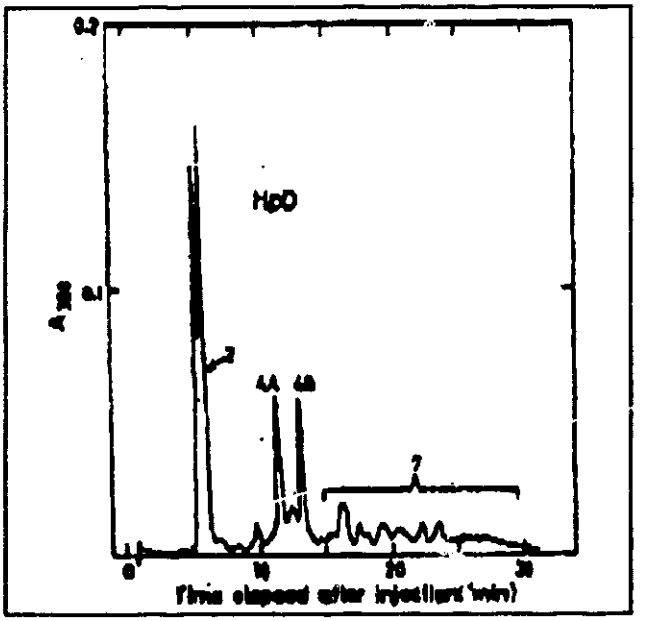


Chart 1, HPLC of HPD; injected volume, 200 µl; concentration, 1 mg/ml; column, Supelcosil LC 15 (250X4.6 mm). Gradient elution with methanol and water. More than 95% of the injected material was eluted during the 40 min run. The components were numbered according to Moan et al. 1983 (infra supra).

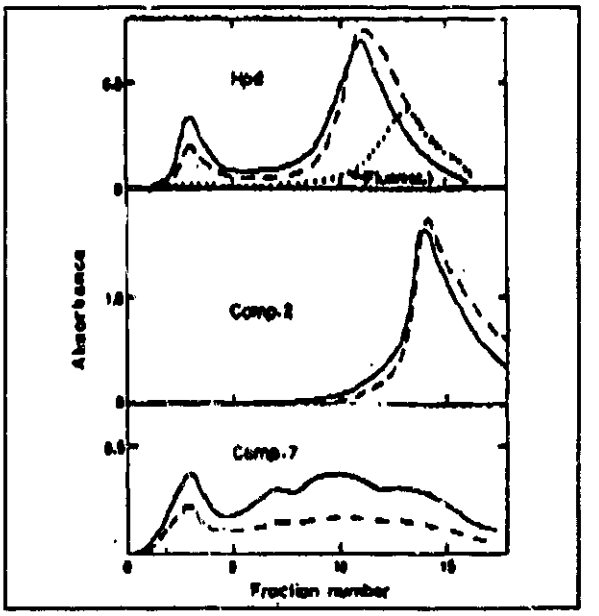


Chart 2, Gel Permeation Chromatography (Bio-Rad P-10 column, 26X1 cm) of HPD and its components 2 and 7. PBS is the mobile phase. Fraction 1 is the first fraction eluted after the void volume of the column has passed. —— absorbance at 360, ---- absorbance at 392, ... fluorescence profile for HPD. The fluorescence intensity was measured at 616 ± 10 nm, the excitation was 396 ± 10 nm.

Everson *et al.* then injected radiolabeled HPD, HP, HP, component 7, $^{3}H_2O$ or ^{67}Ga-citrate, i.v., into mice bearing Lewis lung carcinoma, s.c. Twenty-four hours after the injections they killed the mice and measured the amount of radiolabeled compound in tissue extracts by scintillation counting. The following graph shows that tumor took up twice as much component 7 as it did the other porphyrin components. Component 7 was further purified by gel filtration chromatography. Tumor took up HPD little better than tritiated water, but takes up component 7 almost as well as ^{67}Ga ion. ^{67}Ga concentrates in tumors. The graph also shows that gel fraction 3 (labeled C) accounted for most of the component 7 absorbed by tumor. Fraction 3 contains the largest molecular weight oligomers in component 7. Tumor absorbed the smaller molecular weight fraction (#10, labeled B below) least of any fraction.

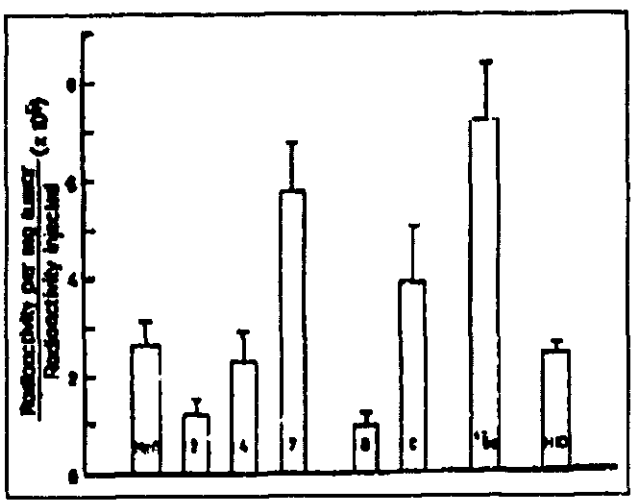


Chart 3, Absolute tumor uptake of ^{67}Ga, $^{3}H_2O$, and ^{3}H-HPD and its components at 24 hours. For definitions of compon-ent 2, 4 and 7 see Chart 1. Component B and C are frac-tions 10 and 3, respectively, from the gel chromatography (Chart 2). For each component, three mice were examined, from each of which three samples from tumor were analyzed. Bars are standard deviation.

The HPLC elution profile of fraction 3 is similar to the radiolabel HPLC elution profile of component 7 extracted from tumor. The investigators also found ten fold higher concentrations of Component 7 in normal mouse liver than in tumor. They also found that liver took up higher concentrations of Component 7 than HPD, HVD or HP. This work probably inspired the addition of the gel filtration step the Photofrin synthetic procedure. This work also shows that tumor fluorescence may not correlate well with PDT efficacy.

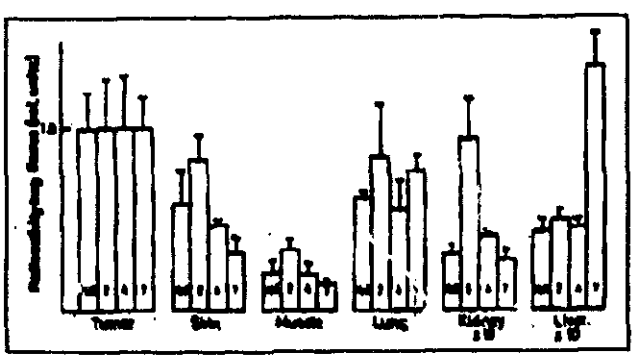


Chart 6. tumor:tissue concentration ratios for HPD and its main comonnents at 24 hours. Three mice were examined for each component. In each mouse three samples from tumor and one sample from each normal tissue were analyzed. Bars show S.D.

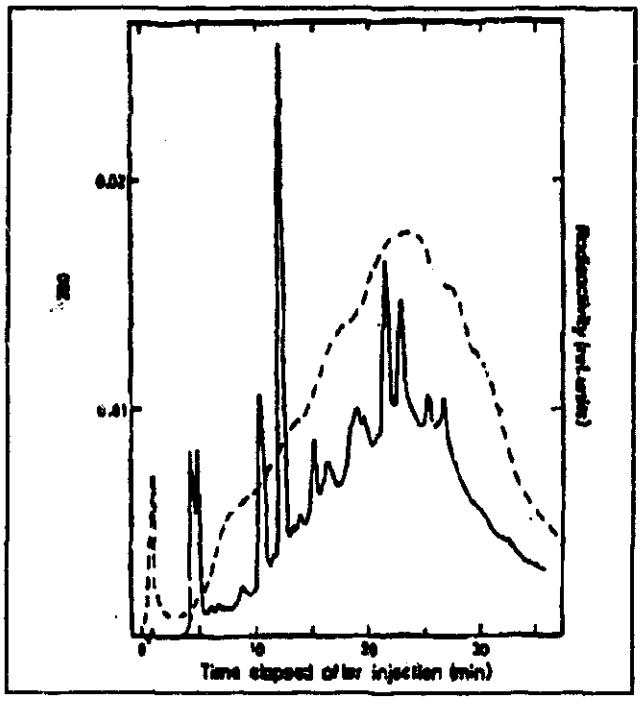


Chart 4. HPLC chromatogram of Fraction 3 from the gel separation (chart 2). ------ profile of radioactivity in the extract of a tumor sample. Conditions were as for Chart 1.

Pharmacology Summary

Photofrin is an anionic lipophilic mixture of ether and ester linked hematoporphyrin oligomers. The length of the oligomeric chain ranges from 2 to 8 or more. The mixture also contains hematoporphyrins, deuteroporphyrin and aggregated porphyrin monomers. These monomers and aggregates are fluorescent but they are not as photoactive as the oligomers. That is, they must be present in higher concentrations to cause the same amount of cell death as the oligomers when irradiated. The oligomers have very low fluorescent quantum yields and are photoactive. The fluorescent transition must be forbidden in these molecules, thus the absorbed energy is available for spin transfer. The monomers and aggregates do not bind to cell membrane as well as the oligomer and cells do not take them up in high concentrations. Some monomers are completely excluded.

When intracellular Photofrin is irradiated with 630 nm light it absorbs photons. The π to π^* transition in the porphyrin ring forms the first excited triplet. Evidently, the oligomer can transfer this energy to an oxygen molecule to form singlet oxygen. Singlet oxygen initiates radical chain reactions. Cell damage accrues from the propagation of these radical chain reaction. The mechanism of singlet oxygen formation is poorly understood. Nevertheless, the role of singlet oxygen has been confirmed several times by incubating cells with singlet oxygen inhibitors or scavengers. Hypoxia caused by a low oxygen tension *in vitro* or by ischemia *in vivo* inhibits Photofrin PDT cytotoxicity. Superoxide ion formation as a result of increased purine degradation secondary to tissue destruction also may contribute indirectly to Photofrin PDT cytotoxicity.

PDT with excimer dye or pulsed lasers causes necrosis more than three times deeper than

continuous argon dye laser, 14.0 mm compared to 4.1 mm. This phenomenon may result from saturation of Photofrin excited states in cells close to the surface.

The cytotoxicity of porphyrins increases with water solubility and with binding to the cell surface. Porphyrin binding to the cell surface inhibits nucleoside and amino acid transport and changes the surface physiochemical properties. Once inside the cell Photofrin-PDT causes damage primarily at internal membranes. Within two hours after PDT cells suffer mitochondrial vacuolization and swelling. Damage to the cell is proportional to the light dose and to the intracellular concentration of Photofrin. Endo-plasmic reticulum, polyribosomes and microtubules are specific targets of PDT damage. Some porphyrins and components of Photofrin bind strongly to membranes. This phenomena has been confirmed by whole cell fluorescence studies. Damage to spindle fibers can retard cells in interphase and prolong metaphase. Photofrin PDT also causes cross-linking of intracellular polypeptides.

Photofrin does not penetrate the nuclear membrane. Damage to DNA is probably due to the propagation of radical chain reactions initiated on the outer surface of the nuclear membrane. The mechanism that repairs this damage is different from DNA repair mechanisms of damage caused by X-rays. Damage is multifocal and nonspecific. Photofrin-PDT can cause DNA-protein cross-links.

Photofrin uptake is time dependant and non-linear. Inhibition of pinocytosis does not prevent Photofrin from entering cells as it does most porphyrin monomers. Photofrin may enter cells by diffusion. Nevertheless, verapamil reduces the efflux of Photofrin after cells have taken up high concentrations. P-glycoprotein expression may decrease the intracellular concentration of Photofrin. However, exclusion of Photofrin by tumor cells expressing p-glycoprotein has not been compared to exclusion by normal parent cell lines. The concentration of Photofrin measured by fluorescence or the presence of a radiolabel varies with tissue type. Photofrin does not cross the intact Blood Brain Barrier in measurable concentrations. Skin, and most epithelium take up Photofrin poorly. Conversely, kidney, lung, spleen and particularly liver usually contain higher Photofrin concentrations than implanted tumors. The concentration of Photofrin inside implanted tumor and the ratio to the concentration in normal tissue is tumor dependant. Thus the efficacy of Photofrin PDT will be tumor dependant. Retardation of tumor growth using Photofrin-PDT with concomitant chemotherapy is additive at best in animal models.

Hyperglycemia before and after PDT increases Photofrin's efficacy. This may be due to increased intracellular pH and the resultant trapping of photofrin. This increased efficacy also may result from increased tumor perfusion and the resultant increased oxygen tension. Photofrin-PDT may cause greater than expected tissue damage in diabetics with elevated blood sugar. Hypoxic radiosensitizers such as misonidazole, MISO, given to tumor bearing mice before or after Photofrin-PDT, delay tumor regrowth. This delay is synergistic with the delay caused by PDT. The increase is 38% greater than the expected additive increase when MISO is added before and 48% when MISO is added 30 min after PDT.

Drugs such as SQ-29548 and R68070 reduced vessel constriction. Flunarizine prevents vessel constriction. SQ-29548 and R68070, but not flunarizine inhibit the PDT associated increase in vascular permeability. All three compounds markedly reduced tumor cures. Thus much of the damage caused by PDT results from vascular constriction, the aggregation of platelets, and clotting. Many tumor cells die from ischemia secondary to coagulation.

Glucocorticoids, such as methylprednisolone acetate and hydrocortisone sodium succinate, increase the efficacy of HPD-PDT. This increased efficacy was measured as a 3 fold increase in the time tumors required to regrow to a predetermined size, TC_{90}. Increasing glucocorticoid dose beyond a compound specific limit does not increase the PDT efficacy. Glucocorticoids given prior to or concomitant with HPD-PDT decrease the tumoricidal efficacy of this therapy. Patients who are taking glucocorticoid hormones may benefit less than expected from Photofrin-PDT. Glucocorticoids did not decrease skin photosensitivity.

Allopurinol inhibits xanthine oxidase. Xanthine oxidase generates superoxide as a by-product of the conversion of free pruines to uric acid. Inhibition of xanthine oxidase results in a decrease in the amount of superoxide generated during the conversion of excess free purines formed by Photofrin PDT damage. Thus allopurinol given before Photofrin PDT can decrease the damage and the effectiveness of the therapy by as much as 90% in animal models. Likewise, Ca^{++}channel blockers, such as verapamil, decrease the concentration of xanthine oxidase and have been shown to decrease damage due to Photofrin-PDT in normal mice. The net effect of Ca^{++}channel blockers in patients receiving Photofrin-PDT is probably tumor specific and dependant on MDR expression.

No direct Photofrin-drug interactions have been documented clinically. Nevertheless, drugs known to cause skin photosensitivity may increase the photosensitivity expected with Photofrin administration. Such drugs include tetracyclines, sulfonamides, phenothiazines, sulfonylurea hypoglycemics, thiazide diuretics and griseofulvin.

Photofrin stimulates hematopoiesis in mice. It caused a 38% increase in white count and leucocyte count by day seven after single dose administration. This increase can be as much as 60 % in the dog. This white cell stimulation causes splenomegaly. The immune system is probably responding to clean up foreign molecules bound to cell surfaces. Tumors frequently contain large numbers of macrophages. It is possible this stimulation could augment Photofrin's tumoricidal efficacy. Immune cells take up large concentrations of Photofrin in normal tissues and in tumors. Immune cells make up as much as 50% of some tumors. These cells may be responsible for part of the ability of tumors to concentrate Photofrin.

Toxicology

32) Farrario A and Gomer CJ. Systemic toxicity in mice induced by localized porphyrin photodynamic therapy. *Cancer Res.* 1990; **50**:539-543.

Ferrario and Gomer implanted pigmented and non-pigmented B16 melanomas s.c. by trochar injec-tion in the shaved right hind leg of mice. When the tumors reached 25 to 35 mm they injected the mice with 10 mg/kg (30 mg/m^2) of Photofrin i.p. Twenty-four hours later they irradiated tumors (1 cm area) with two different power densities of 630 nm light (argon pumped dye laser). The mice suffered unexpect-ed mortality increasing as a function of energy density. The usual clinical dose of Photofrin for human patients is 2 mg/kg (74 mg/m^2) or more than twice the dose used in these experiments. The energy density used in these experiments was 200 to 500 J/cm^2. Light doses in this range are used in some clinical proto-cols. Even more interesting, mouse mortality in these experiments decreased as power density increased from 150 to 600 mW/cm^2. The following table shows percent mortality as a function of light dose and power density.

	% Lethality in C57BL/6J mice							
	Non-Pigmented Tumor				Pigmented Tumor			
Light Dose J/cm^2	150 mW/cm^2	n	600 mW/cm^2	n	150 mW/cm^2	n	600 mW/cm^2	n
200	16.7	12	21.4	14	0	10	0	12
300	52.4	21	23.1	13	33.3	15	0	11
400	54.5	22	16.7	12	41.2	17	9.1	11
500	76.7	43	54.5	22	59.3	27	42.9	21

where n = number of mice. Lethality increased with light dose and decreased with power density when normal mice (no tumor implants) received PDT.

Ferrario and Gomer also measured lethality of PDT (30 mg/m^2 Photofrin , 500 J/cm^2, 150 mW/cm^2) in eight strains of mice. The following table shows that B10D2/NSN and B10D2/OSN mice were resistant to PDT induced lethality.

Mouse Strain	No of Mice	% lethality
C57BL/6	26	77
C3H/HeJ	10	70
$B_{10}D_2$/OSN	20	20
$B_{10}D_2$/NSN	20	0
DBA/2J	9	78
DBA/1J	10	80
BALB/c	10	100
Swiss Webster	10	70

The authors cannot explain these differences. They postulate that the differences may be related to differences in expression of compliment factors C3 and C5 or to altered metabolism and pharmacokinetics of Photofrin.

The researchers gave normal C57BL/6J mice five drugs that affect clotting, warfarin, indomethacin, aspirin, antihistamine and cobra venom factor. The following table shows these results.

	% Lethality in normal C57BL/6J					
Treatment	300 J/cm^2	n	400 J/cm^2	n	500 J/cm^2	n
PDT alone	44	36	61	31	89	54
PDT + warfarin	30	20	50	20	40	20
PDT + indomethacin	5	20	35	20	40	20
PDT + aspirin	20	20	30	20	40	20
PDT + antihistamine	16	32	15	20	35	20
PDT + cobra venom factor	ND		ND		100	10

ND = not determined

Drugs that inhibit cyclooxygenase, histamine release, and coagulation decrease lethality significantly at all energy doses. Cobra venom factor depletes compliment factors C3 and C5. This compound did not significantly alter PDT lethality, implying that that these factors are not involved in causing PDT damage.

PDT (30 mg/m^2 Photofrin, 500 J/cm^2, 150 mW/cm^2) in normal mice caused an elevation in WBC from ~ 10,000 to > 40,000/mm^3 within 4 hours of treatment. WBC then dropped back to normal by day three post treatment. Platelet counts decreased in controls during the first 24 hr post treatment (controls 700,000, treated 500,000/mm^3). Then platelet counts increased to over 900,000/mm^3 by day 7 and remained high through day 15. Recoverable blood volume decreased from 0.63 ml in controls to 0.18 ml in mice receiving PDT. Core body temperature dropped from 35.6 to 25.8 C 24 hr. post PDT.

These results taken together suggest that lethality from PDT in mice is secondary to traumatic

shock. The total surface area of a mouse is between 50 and 70 cm^2. At 150 mW/cm^2, the 1 cm^2 surface area of a mouses leg need be irradiated for 55.5 min to achieve a total dose of 500 J/cm^2. At the higher power density (600 mW/cm^2) the total exposure is less than 14 min for a 500 J/cm^2 light dose. The surface area irradiated was between 1.4 and 2% of the mouses total surface area. Total blood volume in a mouse is about 1.2 ml. Over the course of the PDT most of this small blood volume was exposed to high intensity laser light. Such exposure would be expected to cause hemolysis, clotting and eventually traumatic shock.

These experiments clearly show that PDT to tissue surface areas as small as 1.4% total body area with low intensity light for longer than 15 minutes could be lethal. This area equals a square roughly 15 cm X 15 cm in human adults or slightly larger than the surface area of the urinary bladder. These results argue for well localized treatment, high light intensities and short exposure times. This potential for significant damage to blood and resultant traumatic shock suggests that PDT would be particularly dangerous for patients with thromboembolic conditions, diabetes or sickle cell anemia.

41) Star W *et al.* Destruction of rat mammary tumor and normal tissue microcirculation by hematoporphyrin derivative photoradiation observed *in vivo* in sandwich observation chambers. *Cancer Res.* 1986; 46:2532-2540.

Star *et al.* implanted rats with mammary carcinomas subcutis in transparent observation chambers. They observed microscopic changes in the tumor tissue with time. After exposure to 630 nm laser light the tumors initially blanched due to ischemia secondary to vasoconstriction. The tumor re-perfused, but circulation slowed secondary to vasodilation and eventually stopped. Hemorrhage and necrosis followed this stasis. Platelet aggregated in normal tissue, but the tissue did not become necrotic. Tumor regrowth occurred unless the tumor circulation and the adjacent normal tissue circulation were both destroyed. To assess tumor viability, the researchers removed and re-implanted treated tumor in the same animal. Even after four PDT treatments tumor regrew in five of five animals.

85) Zhou C *et al.* The biological effects of photodynamic therapy on normal skin in mice, I. A light microscopic study. *Adv Exp Med Biol.* 1985; 93:105-109.

In the absence of PDT, 50 mg/kg HPD caused no microscopic changes in the ear skin of mice. Laser light alone caused moderate dilation and congestion of the microvasculature. PDT caused necrosis. Fibroblasts and nerve fibers develop damage soon after PDT, epidermis and chondrocytes respond more slowly.

86) Zhou C *et al.* The biological effects of photodynamic therapy on normal skin in mice,. II. An electron microscopic study. *Adv Exp Med Biol.* 1985; 93:111-115.

At four to six hours after PDT endothelial cells in normal mouse ear skin are swollen. Capillaries are dilated and filled with erythrocytes. At 12 hours capillaries are necrotic. Fibroblast mitochondria are damaged, ribosomes have begun to decrease and vacuoles are forming. Connective tissue is edematous, but collagen fibers are unchanged. Inflammatory cells have infiltrated near capillaries, nerve fibers and muscle. As early as 10 minutes after PDT nerve fibers are swollen and axons contain vacuoles. Mast cells appear within an hour. Severe damage occurs immediately after PDT.

107) Gomer C *et al.* Hematoporphyrin derivative photoradiation therapy for the treatment of intraocular tumors: examination of acute normal ocular tissue toxicity. *Cancer Res.* 1983; 43:721-727.

Gomer *et al* gave HPD, 1 to 10 mg/kg, to normal rabbits. Forty eight hours later they irradiated a 1 cm^2 area of the rabbits retina with 635 ± 5 nm laser light at power densities from 0 to 400 mW/cm^2 for

15 min. They characterized the damage to the retina by fundus photography, fluorescein angiography and histopathology. Damage increased with increasing HPD dose and increasing light energy in a progressing from edema, to detachment to necrosis. Doses of HPD and light less than usual clinical doses caused significant irreversible damage. Retinal damage was limited to the irradiation field at all but the highest doses. PDT damage to the retina is peculiarly severe.

110) Stewart Fa *et al.* Functional and histological damage in the mouse bladder after photodynamic therapy. Br J Cancer. 1992; **65**: 884-890.

Stewart *et al.* gave Photofrin, 10 mg/ml or 30 mg/m^2, to anesthetized mice and irradiated their bladders with 630 nm 24 hours later. The researchers assessed bladder damage by counting the frequency of urination and noting the presence of hematuria at 1 and 26 weeks post treatment. Light doses of 18.75 J/cm^{2}or greater were lethal causing hemorrhage, edema and necrosis. Light doses between 3.75 and 15 J/cm^{2}cause hematuria and frequency in all mice with dose dependant severity. The $ED_{50}$was 6.5 ± 2.3 J/cm^{2}for hematuria. Mice receiving 7.5 J/cm^{2}recovered completely within 10 weeks. Doses above 7.5 J/cm^{2}were associated with focal necrosis and increases incidence of infection. By 6 month most mice had recovered completely with only mild fibrosis of the bladder wall.

111) Yoshida Y *et al.* Photo-activated Photofrin II: astrocytic swelling precedes endothelial injury in rat brain. *J Neuropathol Exp Neurol.* 1992; **51**:91-100.

Yoshida *et al* gave fisher rats Photofrin, 12.5 mg/kg or 37.5 mg/m^2, i.p. They then irradiated an area of brain through a 5 mm craniectomy at different times post dosing. Control rats receiving Photofrin, but no laser irradiation, suffered no histologically observable brain damage. In rats receiving Photofrin and light the researchers saw damage to astrocytes within 1 hour after PDT. At one hour only small amounts of Evans blue (EB) and horseradish peroxidase (HRP) had leaked into the subarachnoid space at the center of the site of laser irradiation. This damage progressed to endothelial cells and then to neurons. They saw thrombi by 18 hours and coagulation necrosis of the exposed area by 48 hr. The authors suggest that these results imply that Photofrin can cross the intact blood brain barrier (BBB).

In most tissues photofrin appears to enter the cell by passive diffusion. It is most unlikely that such a large, charged molecule actually penetrates the BBB by passive diffusion. Yoshida *et al* saw the earliest damage in astrocyte perivascular processes. These processes are the portions of the cell that contact the vascular endothelial cells of the brain capillaries. A basal lamina is imposed between the two cells. Photofrin probably penetrates the vascular endothelial cells, but not the astrocyte. When irradiation then generated radicals, the damage spreads rapidly across the lamina.

The astrocyte compartment is distinct from the neuronal compartment, i.e. these cells form an intermediate barrier compartment between the circulation and the neuron. Astrocytes are phagocytic and they serve to protect the neurons from toxins in the blood. It is also possible that astrocytes in communication with the endothelium take up small amounts of Photofrin, but do not pass it on the neurons. Yoshida *et al* saw significant damage to neurons only after 18 hours. This late damage was probably due to ischemia and coagulation necrosis. If Photofrin actually entered the BBB, the damage to these fragile cells would occur within one to four hours. Concentrations of Photofrin found in whole brain tissue by either fluorescence or radio-label are among the lowest of all tissues. I have found no studies that show the presence of Photofrin in normal neurons. Tumor disrupts the BBB locally. Compounds such as Evans Blue and HRP, excluded by the BBB, distribute freely throughout the interstitium once on neuronal side. This would account for damage seen in normal brain tissue adjacent to tumor in other studies.

117) Shikowitz M. Comparison of pulsed and continuous wave light in photodynamic therapy of papillomas: an experimental study. *Laryngoscope.* 1992; 102:300-310.

Shikowitz infected rabbits with cottontail rabbit papilloma virus (CRPV) on the surface of scarified skin. One month after the development of stable papilloma infection, he gave the rabbits 7.5 mg/kg Photofrin . At varying times he irradiated papillomas with light from a non tunable gold vapor laser (GVL, 628 nm) or a tunable argon pump dye laser (APL, 630 nm).

With the GVL, all papillomas regrew when irradiated with 60 J/cm^2. A light dose of 100 J/cm^2 caused a 72% partial response. 153 J/cm^2 was curative. These results were similar to those seen with the APL. Nevertheless, the response caused by the GVL was much more rapid. At 1 week post treatment all papillomas had responded to PDT with 153 J/cm^2 when irradiated with the GVL. Four weeks passed before all the papillomas responded when irradiated with APL. The progression of this response was linear. Shikowitz does not speculate on the reason for this difference.

Again a pulsed laser caused a better response to PDT than an argon continuous laser. The GVL provides a light pulse for 20 ns at a frequency of 8 to 10 kHz. This frequency is much faster than that of the excimer laser (ref 73). The time between pulses is 0.1 ms, less than the Photofrin triplet half-life. The one property that the GVL and the excimer laser have in common is a photon flux within a pulse that is considerably higher than the flux from the APL. High flux may cause saturation of the p* excited state of porphyrin oligomers close to the tumor surface. The unabsorbed photons could then penetrate to deeper tissue layers. Continuous irradiation probably generates a steady-state between relatively low concen-trations of the p* excited state and high concentrations of the ground state.

123) and 124) are minor amendments to References #125 and #126. QLT acquired the rights to Photofrin from Johnson and Johnson. These amendments note that change in ownership and transfer the archive of the original data to American Cyanamid Company, Pearl River NY.

131) Six week pilot study toxicity study in rats. Protocol 0986/04PF

Animal	♂ and ♀ Sprague-Dawley rats
compounds/doses	0, 5, 10, 15, 20 mg/kg, 5 rats/sex/dose
Drug	Photofrin (Lot PC225) in 0.9% sterile saline
Light intensity	20 foot candles in cage, 40 to 60 front of cage.
administration	i.v., 1 dose/week
Evaluation	mortality
	Clinical signs at dosing and twice daily
	Body weight weekly
	food consumption weekly
	clinical chemistry, hematology before necropsy
	post mortem (day 14), organ weights, histopathology
Investigators	Photomedica Inc. Raritan, N.J.
GLP	No statement found

Photomedica terminated the study early, five weeks and four days for females, five weeks and five days for males. No rats died on study at any dose. Body weights of treated rats were statistically equal to controls. High dose females consumed less food than controls in the last week of the study, ~10% decrease.

All mice in the high dose group had urine stained hair. Four of five high dose females suffered alopecia by week three. Ear edema increased with time from week one with dose.

Consistent with the ref # 122 WBC increased with dose in males and females. The increase was over 2X in animals dosed with 20 mg/kg. The values for animals dosed with 5 and 10 mg/kg were over 20000/mm^3 (normal 5,3,000 to 14,900/mm^3). Hemoglobin and hematocrit decreased with dose, about 20% in high dose males, 10% in females. BUN tended to be lower in females with dose, the difference was signi-ficant in the high dose group, ~20% decrease. SGOT, AP and SGPT increased with dose in females, as high as 100% in the high dose group.

The following table shows the incidence of the only significant gross findings at necropsy, enlargement of the submaxillary glands in females and enlargement of all lymph nodes in males. These findings are consistent with the immune stimulation described above.

	submaxillary gland	
sex	dose mg/kg	number/total
F	0	0/5
F	5	0/5
F	10	2/5
F	15	1/5
F	20	2/5
	Lymph node enlargement	
M	0	0/5
M	5	0/5
M	10	1/5
M	15	5/5
M	20	5/5

Doses of 15 mg/kg given once per week for five weeks cause measurable toxicity in the rat. This study successfully established the range for a more comprehensive thirteen week study. This 13 week study was reviewed by Dr. Taylor in January of 1989. His review is appended. The results of this pilot study predict many of the results of the 13 week study. Long term Photofrin administration alters liver function particularly in females. Photofrin causes immune stimulation. Some of the changes observed in the 13 week study were irreversible at 8 weeks recovery, i.e. organ weight changes.

157) Schwartz CS. A single dose, acute oral (gavage) lethality study of CL 85,432 (Photofrin intermediate) in rats (study 90188). Pearl River, NY: 1991; 1-10.

Animal	♂ and ♀ Sprague-Dawley rats
compounds/doses	2000 mg/kg, 5 rats/sex/dose, no control
Drug	hematoporphyrin dihydrochloride (CAS 17696-69-4) Batch 13711B-147, purity 73.8% in 0.5% Methocel with 0.1%Tween 80
Light intensity	not specified
administration	p.o. single dose gavage
Evaluation	mortality Clinical signs at dosing and twice daily for two weeks Body weight weekly post mortem (day 14)
Investigators	Cyanamid, Pearl River NY
GLP	Statement included and signed.

Hematoporphyrin dihydrochloride, HP, is an isolated intermediate in the synthesis of Photofrin. It elutes in the last major fraction from gel filtration but is found in significant quantities in Photofrin. HP is the major fluorescent component of Photofrin.

None of the rats in this study died. Females lost an insignificant amount of weight in the first week after dosing but recovered by study end. None of the rats showed gross changes at necropsy.

This very high dose of HP was probably poorly absorbed. Most of the compound was probably excreted in the first 24 hours. HP is not very toxic at this dose, but this study is not informative.

158) Schwartz CS. A single dose, acute dermal lethality study of CL 85,432 (Photofrin intermediate) in rabbits (study 90190). Pearl River, NY: 1991; 1-15.

Animal	♂ and ♀ New Zealand white rabbits
compounds/doses	2000 mg/kg, 5 rabbits/sex/dose, no control
Drug	hematoporphyrin dihydrochloride (CAS 17696-69-4) Batch 13711B-147 purity 73.8% in paste, 1 part HP 2 parts normal saline (w/v)
Light level	12 hr normal cycle
administration	topical, 24 hr under dressing
Evaluation	mortality Clinical signs at dosing and twice daily for two weeks dermal irritation d2 and d4, Primary Irritation Index (PII) Body weight weekly post mortem (day 14)
Investigators	Cyanamid, Pearl River NY
GLP	Statement included and signed.

No rabbits died during this study. HP burned small non-healing holes through the dermis and epidermis directly under the dosing site. The males suffered no erythema or edema around these lesions. Females suffered slight edema and slight to well defined erythema around the dosing site. The investigators estimated the PII in males to be 0.0 and in females 0.9. They observed no other clinical symptoms or gross lesions. The rabbits gained weight normally. Topically applied HP causes local lesions, but no grossly observable systemic toxicity.

160) Schwartz CS. A single dose, acute oral (gavage) lethality study of CL 184,295 (Photofrin intermediate) in rats (Study No. 90189). Pearl River, NY: 1991;1-10.

Animal	♂ and ♀ Sprague-Dawley rats
compounds/doses	2000 mg/kg, 5 rats/sex/dose, no control
Drug	hematoporphyrin diacetate (CAS 69423-76-3) Batch PC1013 purity 38.6% in 0.5% Methocel with 0.1%Tween 80
Light level	12 hr normal cycle
administration	p.o. single dose gavage
Evaluation	mortality Clinical signs at dosing and twice daily for two weeks Body weight weekly post mortem (day 14)
Investigators	Cyanamid, Pearl River NY
GLP	Statement included and signed.

Hematoporphyrin diacetate, HPa, is an isolated intermediate in the synthesis of Photofrin. It elutes in the last major fraction from gel filtration but is found in significant quantities in Photofrin.

None of the rats in this study died. Females lost an insignificant amount of weight in the first week after dosing but recovered by study end. Males gained weight normally. None of the rats showed gross changes at necropsy.

This very high dose of HPa was probably poorly absorbed. Most of the compound was probably excreted in the first 24 hours. HPa is not significantly toxic at this dose.

161) Schwartz CS. A single dose, acute dermal lethality study of CL 184,295 (Photofrin intermediate) in rabbits (Study No. 90191). Pearl River, NY: 1991;1-12.

Animal	♂ and ♀ New Zealand white rabbits
compounds/doses	2000 mg/kg, 5 rabbits/sex/dose, no control
Drug	hematoporphyrin diacetate (CAS 69423-76-3) Batch PC1013 purity 38.6% in paste, 1 part HPa 2 parts normal saline (w/v)
Light level	12 hr normal cycle
administration	topical, 24 hr under occlusive dressing
Evaluation	mortality Clinical signs at dosing and twice daily for two weeks dermal irritation d2 and d4, Primary Irritation Index (PII) Body weight weekly post mortem (day 14)
Investigators	Cyanamid, Pearl River NY
GLP	Statement included and signed.

No rabbits died during this study. HPa did not cause the small non-healing holes directly under the dosing site caused by HP. The rabbits suffered no erythema or edema around these lesions. The investigators estimated the PII in males to be 0.1 and in females 0.0. They observed no other clinical symptoms or gross lesions. The rabbits gained weight normally. Topically applied HPa at 2000 mg/kg no grossly observable systemic toxicity or irritation. This results suggests that the lesions resulting from topical application of HP resulted from the hydrochloric acid and not from the porphyrin.

162) Schwartz CS. A primary ocular irritation (POE) study of CL 184,295 (Photofrin intermediate) in the rabbit (Study No. 90195). Pearl River, NY: 1991;1-12.

Animal	♂ and ♀ New Zealand white rabbits
compounds/doses	0.1 g/right eye, 4 rabbits, left eye control
Drug	hematoporphyrin diacetate (CAS 69423-76-3) Batch PC1013 purity 38.6%, 100% powder.
Light level	12 hr normal cycle
administration	topical, 24 hr under occlusive dressing
Evaluation	Clinical signs at dosing and twice daily for two weeks ocular irritation 1, 24, 48, 72 hrs. Body weight before and after study
Investigators	Cyanamid, Pearl River NY
GLP	Statement included and signed.

No rabbits died in this study. The rabbits gained weight normally. HPa caused conjunctival

redness (Draize scores 1 or 2) in all rabbits at 24 hours. Three of the four rabbits had an iridial score of 1 at 24 hours. This irritation was reversible. The rabbits suffered irritation even when the researchers washed out the HPa. Dry HPa is an eye irritant. At this dose the eye damage is probably mechanical.

Toxicology Summary

Without light activation, high doses of i.v. Photofrin are well tolerated. The MTD in mice has been estimated at 100 mg/kg or 300 mg/m^2. Only one mouse in 10 died at 125 mg/kg. For comparison, the clinical dose is 2.0 to 2.5 mg/kg or 74 to 92.5 mg/m^2. Thus, the human therapeutic dose is one third the mouse MTD. Higher doses do not improve the efficacy of photodynamic therapy. Some tumors treated with Photofrin alone showed focal swelling and focal mitochondrial vacuolization. Some normal endothelial cells will also show this focal swelling after high doses of Photofrin.

Rats show similar tolerance to high doses. Eight of 10 died at 100 mg/kg or 590 mg/m^{2}three to five days post dosing. None died at lower doses. During the first three hours after dosing, these rats suffered piloerection, jerking or writhing, labored breathing, hypothermia, and decreased activity. Subsequently the animals suffered anorexia and weight loss and were in poor physical condition. High doses Photofrin causes enlargement of the liver and spleen, increased erythropoiesis and hemosiderin deposition in the liver and spleen. Lethal doses cause intravascular hemolysis and the accumulation of RBC debris in the liver, centro-lobular necrosis of the liver, lymphoid depletion or necrosis in the lymph nodes, spleen and thymus, myofiber necrosis and ischemic necrosis in the renal cortex.

An acute dose of 50 mg/kg (1000 mg/m^2, i.v.) was lethal to one of two dogs, 100 mg/kg killed two of two. 25 mg/kg caused immediate emesis. Photofrin caused a 20 to 66% increase in WBC and a 10 to 17 % decrease in RBC, Hbg and Hct in dogs receiving doses between 25 and 100 mg/kg. Increases in GOT, ALP seen by day seven in surviving dogs returned to normal. Photofrin caused splenomegaly at all three doses.

Photofrin is more toxic when areas of skin are exposed to light. Seven of ten mice died one day after a three hour exposure to 120 foot candles (fc) of light then a normal 12 hour cycle of room light (4 to 19 foot candles) at a Photofrin dose of 50 mg/kg (150 mg/m^2). A dose of 100 mg/kg killed all mice at this high light exposure. Mice dosed with less than 50 mg/kg suffered alopecia, scab formation on the head and ears, edema and erythema and piloerection. The symptoms were those of a severe sunburn. Deaths within the first day was caused by edema and fluid imbalance secondary to membrane disruption and cell damage. In a similar study, nine of 10 rats died within 24 hr after receiving 80 mg/kg Photofrin and a light dose of 160 fc followed by normal light cycle. Rats given 60 mg/kg Photofrin suffered severe erythema, burns and eye damage with light doses as low as 60 fc for 3 hr. Normal room illumination caused no damage at this high dose. When investigators gave rats 60 mg/kg of Photofrin, they remained photosensitive for as much as 12 weeks after dosing. High light doses concurrent with photofrin administration cause irreversible damage to the retina. Photofrin powder is an ocular irritant.

Rats given Photofrin i.v. weekly for 13 weeks suffered reversible anorexia and weight loss at doses above 10 mg/kg or 59 mg/m^2. Doses to 20 mg/kg or 118 mg/m^{2}were not lethal. RBC, Hct and Hgb decreased with dose 2 to 3 fold, while WBC and reticulocytes increased with dose about two fold. These changes in white cell counts were not completely reversible at eight weeks. Consistent with the damage to the liver noted above ALT, AST, AP and cholesterol increase with time and dose. Sub-acute photofrin caused increases in the relative weights of liver, spleen, heart, lung, kidney, brain, ovary and testes. Again these changes were not completely reversible at eight weeks. Photofrin was deposited as a brown pigment in macrophages of the spleen, lymph nodes, and bone marrow and in Kupffer cells. It

causes hyperplasia of the bile ducts and lymphoid tissues in the spleen. These changes appear to resolve but slowly. Dogs respond to sub-acute Photofrin administration with a similar spectrum of toxicities at doses to 200 mg/m^2 without mortality.

Photofrin causes concentration dependent hemolysis in normal human blood ex vivo, 13.1% at 50 µg/ml. Exposure to 158 fc for one hr increases this hemolysis up to seven fold. Repeated challenge does not cause an antibody response in mice. The clinical formulation of Photofrin does not cause ocular irritation in rabbits. Photofrin, 2.5 mg/ml, did not cause protein flocculation in human plasma. Rabbit skin is not significantly irritated by Photofrin powder after a 24 hr application.

Only doses of Photofrin that caused toxicity in the mother (4 and 8 mg/kg/d) caused fetal abnormalities in pregnant rats during fetal organogenesis, days seven to 17. These abnormalities included increased resorptions, decreased litter size, reduced fetal weight. Other changes were minor, there were no major malformations or developmental changes. Photofrin causes similar minor gestational abnormalities in rabbits. Photofrin given to rats before conception caused no toxic symptoms at 1.0 and 0.5 mg/kg/d for females and males respectively. Photofrin dosing does cause hypertrophy of the ovaries and testes.

Phototoxicity increases with light dose. Nevertheless, short exposures to high intensity light are less toxic than longer exposures to low intensity light at the same power density. This is because longer exposure damages greater numbers of RBCs flowing through the irradiated tissue. Phototoxicity also increases with increased light exposed surface area, again because more blood is exposed. Exposure of about 1.4% of total external surface area of mice to 300 J/cm^2 was lethal to half. Susceptibility of mice to phototoxicity is strain dependant. Drugs that inhibit cyclooxygenase, histamine release and coagulation decrease lethality due to phototoxicity.

Genotoxicity

159) Stankowski LF. Ames/*Salmonella* plate incorporation assay on CL 85,432-hematoporphyrin dihydrochloride (study 90206). Pharmakon Research International, Inc, Waverly, PA: 1991; 1-17.

Test Strains	Salmonella typhimurium - TA1535, TA1537, TA1538, TA98, TA100
compounds/doses	50, 167, 500, 1670 and 5000 µg/plate
Drug	hematoporphyrin dihydrochloride (CAS 17696-69-4) Batch 13711B-147, purity 73.8%
Solvent	DMSO
Negative control	DMSO
Positive control	9-aminoacridine, 2-nitrofluorene, anthramine, sodium azide
Activation	S9, rat liver Aroclor 1254 induction
Light level	dark
administration	48 hr exposure
GLP	Statement included and signed.

HP precipitated at doses of 1670 and 5000 µg/plate. All cultures grew normally. None of the treatments with HP, with or without S9, cause > 2 fold increase in revertants. Positive controls produced the antici-pated response. HP was not mutagenic in the Ames assay. HP probably did not cross the bacterial cell wall.

163) Stankowski L. Ames/*Salmonella* plate incorporation assay on CL 184,295 - hematoporphyrin diacetate (Study No. 90207). Pharmakon Research International, Inc, Waverly, PA: 1991;1-18.

Test Strains	*Salmonella* typhimurium - TA1535, TA1537, TA1538, TA98, TA100
compounds/doses	16.7, 50, 167, 500, 1670 and 5000 µg/plate
Drug	hematoporphyrin diacetate (CAS 69423-76-3) Batch PC1013, purity 38.6%
Solvent	DMSO
Negative control	DMSO
Positive control	9-aminoacridine, 2-nitrofluorene, anthramine, sodium azide
Activation	S9, rat liver Aroclor 1254 induction
Light level	dark
administration	48 hr exposure
GLP	Statement included and signed.

HPa precipitated at doses of 5000 µg/plate. All cultures grew normally. All cultures incubated with HPa, with and without S9, produced fewer or approximately the same number of revertants as negative controls. Positive controls produced the anticipated response. HPa was not mutagenic in the Ames assay. HPa probably did not cross the bacterial cell wall.

171) Thilagar A. Test for induction of gene mutation at the HGPRT locus in cultured Chinese hamster ovary (CHO) cells with and without photoactivation on Photofrin II, (Study No 89051). Pearl River, NY: 1989: GT:265-304.

CHO cells	Confirmed by karyotype
Positive Control non-activated	Ethyl methane sulfonate (EMS) 0.5 µl/ml final, in DMSO
Positive Control activated	7,12-dimethylbenz(a)anthracene (DBMA) 5.0 µg/ml total, solvent acetone
Photofrin Solvent Control	Saline
Activation System	Aroclor 1254 induced male rat liver S9
Treatment light	White light fluorescent bulbs
Treatment time	5 hours
Selection Compound	6-Thioguanine (TG) 10 µM
Photofrin lot number	PC258C

The title of this experiment is somewhat misleading. Thilagar determined the induction of mutations in CHO cells at the hypoxanthine guanine phosphoribosyl transferase (HGPRT) locus at fixed doses of Photofrin and varying light energy density. He determined only the cytotoxicity of Photofrin at varying concentrations in the absence of light. He determined the mutation rate as a function of total energy density in cell systems treated with and without S9. In the S9 activated system, the Photofrin concentration was 50 µg/ml, without S9 the Photofrin concentration was 10 µg/ml. Thilagar based these concentrations on the results of a range finding study. The following table shows the cytotoxicity resulting from increasing Photofrin concentrations in the dark.

Range finding experiment showing Photofrin Cytotoxicity

Without S9 Activation				With S9 Activation			
Photofrin conc. µg/ml	Ave # Colonies	sd	RCE	Photofrin conc. µg/ml	Ave # Colonies	sd	RCE
Negative Control	187	21.5	94%	Negative Control	187	28.2	101%
Solvent Control	198	18.4	100%	Solvent Control	186	11.8	100%
0.2	203	5.2	103%	12.5	198	5.9	106%
1	206	7.2	104%	25	200	14.4	108%
5	202	8.6	102%	50	196	9.3	105%
10	219	7.2	111%	75	172	24.3	92%
15	178	13.2	90%	100	148	17.5	80%
20	167	5.2	84%	150	153	14.1	82%
25	151	5.4	76%	200	139	14	75%
				250	126	5.2	68%

RCE = Average # of colonies per plate / average # of colonies per control plate

At a constant Photofrin concentration of 10 µg/ml and without S9 activation, light doses of 420, 525, and 630 J/cm^2 caused so much cell death that the system could not be cultured in the selection media for mutants. At a Photofrin concentration of 50 µg/ml and with S9, light doses of 525 and 630 J/cm^2 were too toxic. The following table shows the results of the mutation assay at constant Photofrin concentrations and varying energy densities.

HPGRT mutation in CHO cells incubated with constant Photofrin concentrations

Without S9 Activation, Photofrin 10 µg/ml				With S9 Activation, Photofrin 50 µg/ml			
Light energy density J/m2	Ave # Colonies	RCE	ave mutants /10^6 cells	Light energy density J/m2	Ave # Colonies	RCE	ave mutants /10^6 cells
Negative Control	217	121%	16	Negative Control	215	110%	9
solvent control	179	99%	20	solvent control	187	96%	8
Solvent Control + 630 J/m2	180	100%	16	Solvent Control + 630 J/m2	195	100%	10
0	155	86%	5	0	162	83%	2
35	165	92%	1	105	117	60%	10
70	131	73%	4	210	75	38%	0
105	105	58%	4	315	32	16%	0
210	43	24%	28	420	16	8%	0
315	9	5%	nd				
EMS Solvent	171	100%		DMBA Solvent	163	100%	2
EMS	82	48%		DMBA	114	70%	450

Photofrin did not cause any significant increase in mutation rate above control when the data was analyzed by Students t, trend test or ANOVA. At the Photofrin concentration used in the non-activated system the absorbance of the test solution is well above 1 (Soret maximum), in the activated system it is greater than 6. The author does not mention this problem, but both test solutions were practically opaque. Little light could have reached the cells at low energy density and the concentrations were not cytotoxic. In the non-activated system, the highest light dose tested (210 J/m^2) caused 24% cell death and an obvious, though less than two fold increase in mutations. The difference between the number of mutations caused by this light dose and that caused by the solvent control is not significant because the standard deviations for both experiments are high. Nevertheless, this result suggests that the range of these experiments may not be adequate. Though well conducted these experiments are poorly designed and provide no useful information about the genotoxicity of Photofrin.

No experiments have shown that cytochrome P-450 1A1 or other isozymes induced by Aroclor oxidize or reduce Photofrin. Thus the relevance of S9 activation is unknown. Nevertheless, the difference in Photofrin toxicity between the activated and non-activated system suggests that S9 causes the formation of a less toxic product. This was a GLP study.

The sponsor should conduct experiments quantifying mutations caused by three to five concentrations of Photofrin in the absence of light with and without S9 activation. The highest concentration of Photofrin should be significantly cytotoxic, i.e. allowing between only 10 and 30 % cell survival. To determine the effect of light on the mutation rate the sponsor should conduct a similar set of experiments at several Photofrin concentrations where the cells are washed after incubation with Photofrin and prior to exposure to light.

172) Thilagar A. Test for induction of chromosome aberration with Photofrin (CL 184,116) using monolayer cultures of Chinese hamster ovary (CHO) cells with and without metabolic activation (Study No 89050).

CHO cells	Confirmed by Karyotype
Positive Control non-activated	tetraethylene amine (TEM) 1.0 µl/ml total
Positive Control activated	Cyclophosphamide (CP) 50 µg/ml total
Photofrin Solvent Control	isotonic saline
Activation System	Aroclor 1254 induced male rat liver S9
Treatment light	White light fluorescent bulbs
Treatment time	5 hours
Photofrin lot number	PC258C

Thilagar determined the number of chromosome aberrations caused by Photofrin with and without light activation at different energy densities and with and without S9 in CHO cells. Again he irradiated the cells in the presence of high concentrations of Photofrin, thus the solutions were again opaque. Based on a range finding study Thilagar chose Photofrin concentrations of 3 µg/ml for the non-activated systems and 25 µg/ml for the S9 activated system. These concentrations were cytotoxic to less than 10% of the cells. He irradiated the cells with 0 to 630 J/cm^2, white light. Again the S9 system is less toxic. Photofrin caused no increase in the incidence of chromosome aberration in CHO cells above controls. This was a GLP study but it provides little or no information about the genotoxicity of Photofrin.

173) Thilagar A. Test for induction of sister chromatid exchange with Photofrin II (CL 814,116) in cultured Chinese hamster ovary (CHO) cells with and without exposure to light (Study No 89049).

CHO cells	Confirmed by Karyotype
Positive Control non-activated	tetraethylene amine (TEM) 0.025 µl/ml total
Positive Control activated	Cyclophosphamide (CP) 2.5 µg/ml total
Photofrin Solvent Control	isotonic saline
Activation System	Aroclor 1254 induced male rat liver S9
Treatment light	White light fluorescent bulbs
Treatment time	5 hours
Photofrin lot number	PC258C

Thilagar determined Photofrin's ability to cause sister chromatid exchange (SCE) in CHO cells with and without S9 activation. He varied light exposure from 0 to 630 J/m^2 white light. Based on a range finding study Thilagar chose Photofrin concentrations of 2 µg/ml for the non-activated systems and 15 µg/ml for activated system. Again, in these experiments the cells were irradiated in the presence of the Photofrin solution, so the light could not have reached the cells. Again the Photofrin concentrations were not significantly cytotoxic.

The S9 decreases Photofrin's toxicity. Photofrin caused a small but statistically significant increase in the incidence of SCE in CHO cells when irradiated with light and activated with S9. The following table shows these results.

Treatment	[Photofrin] µg/ml	Light J/m²	mean SCE/cell	p-value
Positive control	0	0	56.08	< 0.1
Untreated control	0	0	14.12	-
Light control	15	0	16.20	-
Saline control	0	630	16.78	-
Treated	15	315	19.38	0.25
Treated	15	420	21.28	< 0.1
Treated	15	525	21.40	< 0.1
Treated	15	630	23.00	< 0.1

The greatest increase is about 1.4 fold. The test for a positive trend (one tailed ordinal trend) is significant to $p < 0.001$.

Without S9 activation, Photofrin also caused an increase in SCE above controls. Again these increases were less than 2 fold but were significant. The following table shows these results:

Treatment	[Photofrin] µg/ml	Light J/m²	mean SCE/cell	p-value
Positive control	0	0	40.64	< 0.01
Untreated control	0	0	11.12	-
Light control	2	0	11.20	-
Saline control	0	525	11.48	-
Treated	2	210	14.28	< 0.01
Treated	2	315	16.10	< 0.01
Treated	2	420	17.08	< 0.01
Treated	2	525	17.56	< 0.01

Again the test for a positive trend is significant to $p < 0.001$. These results suggest a potential for genetic toxicity, even though Photofrin caused an increases in SCE < two fold. The design of these experiments may seriously underestimate the genotoxicity of Photofrin with and without light. The activated and non-activated system caused chromosomal damage at concentrations that could well be reached in organs such as the liver. This suggests that irradiation of organs that concentrate Photofrin should be avoided during PDT. This was a GLP study.

Again the sponsor should repeat these experiments using three to five concentrations of Photofrin, the highest of which should be significantly cytotoxic. The Photofrin should be washed from the cells prior to irradiation. Other non GLP studies have suggested that Photofrin may cause significant SCE, thus a well conducted GLP study of this particular chromosome aberration is particularly important.

174) Manandhar M. Micronucleus test on Photofrin II (CL 184,116) administered intravenously to male mice (Study No 89052). Pearl River, NY: 1989; GT7:211-240.

Manandhar gave Photofrin to CD-1 mice i.v., 0, 7.5, 25, and 75 mg/kg single dose. He gave positive control mice triethylenemelamine, 1.0 mg/kg, i.p. At 24, 48, and 72 hours post dosing he killed groups of ten mice from each dosing group. By microscopic examination he scored the bone marrow for the presence of micronucleated polychromatic erythrocytes in each group.

None of the mice displayed clinical symptoms associated with the Photofrin dose. Photofrin caused no significant increase in the incidence of micronucleated polychromatic erythrocytes above

negative controls. Triethylenemelamine did. This was a GLP study.

175) Gomer C, *et al.* Transformation and mutagenic potential of porphyrin photodynamic therapy in mammalian cells. *Int J Radiat Biol.* 1988;53(4):651-660.

Gomer *et al.* determined that Photofrin does not increase the number of Chinese hamster lung fibroblasts resistant to ouabain by mutation. They irradiated the cells with 570 to 650 nm light at energies from 0 to 525 J/cm^2. These researchers rinsed the cells after a 16 hour exposure to Photofrin and prior to irradiation, so these results are considerably more useful than those in the studies by Thilagar. Gomer *et al.* used UV irradiation as a positive control, 254 nm. They dosed the cells with 25 µg/ml of Photofrin or HPD. Again this concentration was not significantly cytotoxic.

181) Kvam E, *et al.* The lengths of DNA fragments light-induced in the presence of a photosensitizer localized at the nuclear membrane of human cells. *Biochim Biophys Acta.* 1990;**1049**:33-37.

Kvam *et al.* used Photofrin as a probe to determine the average length of DNA in chromatin fibers. They assumed Photofrin did not enter the nucleus but bound to the nuclear membrane. Thus damage to the DNA must be caused at the inner surface of the nuclear membrane. Here sections of folded DNA are in close contact. They measured DNA damage by determining the decrease in Hoechst 33258 fluorescence with light dose in cells laden with Photofrin. Hoechst 33258 fluorescence is proportional to the concentration of double stranded DNA. It does not bind to unwound or damaged DNA. Kvam *et al.* determined that the mean length of a fragment, assumed to represent a fold, is 155 kilobases in NHIK 3025 carcinoma cells. The length of the fragments fit a Γ distribution. Despite the fact that Photofrin does not cross the nuclear membrane, this research does imply that it can cause DNA strand breaks.

185) Tan JC, *et al.* Effects of radiation and porphyrin on mitosis and chromosomes in human hematopoietic cell lines. *J Med.* 1976;7(2):169-176.

Hematoporphyrin did not cause an increase in chromosome breaks or aberrations in human hematopoietic cell lines, RPMI-1788 or Kujenick cells, *in vitro*.

195) Williams GM. Review of genotoxicity studies of Photofrin. American Health Foundation, Valhalla, NY. 1993; 1-20.

Williams has surveyed the literature for studies of the genotoxicity of Photofrin and HPD. I or the previous pharmacology reviewers of Photofrin have already commented on most of the studies Williams has considered.

Genotoxicity Summary

Photofrin in the presence of light causes DNA single and double strand breaks in cells in culture, study 181. Sodium Azide, a singlet oxygen scavenger, prevents this damage. This damage is repairable and is usually not the cause of cell destruction. Most damage is at guanine residues, again pointing to a singlet oxygen mechanism. Photofrin with 630 nm light causes inactivation of lysosomal, mitochondrial and cytosolic enzymes. It also causes a decrease in intracellular ATP and glutathione. Because less Photofrin reaches the nuclear membrane than other membranes and because DNA damage is repairable, damage outside the nuclear membrane is usually responsible for cell death. S9 metabolic activation decreases the cytotoxicity of Photofrin with or without light. The metabolite responsible for this decrease has not been identified.

Photofrin plus light with or without S9 activation did not cause reversion mutations at the Salmonella/histidine locus of five tested strains, TA1535, TA1537, TA1538, TA98, and TA100 up to 5 mg/plate. Neither did it cause mutations at the E. coli/tryptophan locus of WP2-uvrA with light or activation (169 & 170). Nevertheless, bacteria may not absorb Photofrin. No one has studied bacterial absorption of Photofrin.

In GLP genotoxicity tests, Photofrin did not cause mutations at the HGPRT locus of Chinese hamster ovary (CHO) cells at 10 µg/ml without S9 activation or 50 µg/ml with S9 both irradiated at 315 J/m^2(171). Higher light doses were cytotoxic. Photofrin did not cause chromosome aberrations in CHO cells with or with out light to 630 J/m^2. In this test the photofrin concentration was 3 µg/ml in the non-activated system, 25 µg/ml in the activated system (172). Photofrin with and without S9 activation caused small but statistically significant increases in sister chromatid exchange in CHO cells irradiated to 630 J/m^2. The Photofrin concentrations used in these tests were 2 µg/ml in the non-activated system, 15 µg/ml in the activated system. In all cases the increases in mean SCE/cell were two fold or less above control so these tests suggest that Photofrin is not significantly mutagenic (173). Nevertheless, none of these three studies assessed the mutagenicity of Photofrin in the absence of light at more than one concentration, and none of the concentrations tested were significantly cytotoxic. In all three studies tested cell cultures were irradiated while still covered with the Photofrin test solution. The concentrations of these test solutions were so high that they must have been opaque, though the investigator does not describe this problem. Thus, little light likely reached the test cells except at very high energy densities. High energy densities were cytotoxic and in the case of the HGPRT test results suggest an increase in muta-tions at the highest light dose. The HGPRT test and the SCE test should be repeated using cytotoxic Photofrin concentrations and a wash step. Photofrin did not cause chromosomal aberrations in mice *in vivo* at 75 mg/kg i.v., mouse micronucleus test (174). At the clinical dose the whole body concentration of Photofrin is between 2 and 3 µg/ml or higher, especially in reticuloendothelial tissues.

In non-standard published genotoxicity tests, Photofrin plus light caused an increase in the number of thymidine kinase (TK) mutants in mouse L5178Y strains LYSI (1.5/1000 cells) and LYR16 (2.2/1000 cells) under conditions that killed 63% of the cells (study 176). PDT with Photofrin did not mutate LYR83, a hemizygous strain. This suggests that Photofrin causes multi-locus mutations. X-radiation caused 1.7 mutations/1000 cells in LYSI under similar conditions.

When irradiated with short wavelength light, Photofrin caused a 3 fold increase in the frequency of sister chromatid exchange in Chinese Hamster lung fibroblasts (study 179). Nevertheless, this result could be the result of the mutagenicity of 5-bromodeoxyuridine (BDU) used in these assays or the unusual light wavelength. The protocol for this study was unusual.

Photofrin-PDT at short wavelengths (blue light) caused an unspecified increase in DNA-Protein cross-links in mouse lymphoma L5178Y cells. This damage was determined by DNA retention on nitrocellulose (study 182). Photofrin did not cause chromosome aberrations with or without light in normal cell lines. It did cause a light dose dependant increase in DNA-strand breaks in a malignant cell line (human NHIK 3025 cervical carcinoma, study 181).

These studies taken together demonstrate that Photofrin plus high intensity light can cause DNA strand breaks. This damage probably results from the propagation of free radical chain reactions across the nuclear membrane. A non-standard SCE study suggests that Photofrin is mutagenic by the usual criterion of a two fold or greater increase in mutation above control. The standard GLP assays in mammalian cells are inconclusive or were conducted under inappropriate conditions. These studies should be redone. Nevertheless, Photofrin is considerably less genotoxic than most cancer chemotherapeutic agents, its effects are difficult to detect. These studies also suggest that genetic damage is not the primary mechanism of Photofrin-PDT cytotoxicity.

Absorption, Distribution, Metabolism and Elimination.

35) Kongshaug M *et al.* Distribution of porphyrins with different tumor localizing ability among human plasma proteins. *Brit J Cancer.* 1989; 59:184-188.

Kongshaug *et al.* mixed protoporphyrin (PPIX), hematoporphyrin (HP), Photofrin, and tetraphenyl porphine sulfonates ($TPPS_{1,4}$) with human plasma. They separated the fractions by CeCl gradient centrifugation and by size exclusion chromatography. They found that more lipophilic porphyrins bound strongly to LDL, 30 % for $TPPS_1$. Water soluble porphyrins such as Photofrin and PPIX bound less strongly, 16% and 9% respectively. Water soluble porphyrins bound more readily to HDL and serum albumin. Most Photofrin bound HDL, 70%, fourteen percent bound serum albumin. The researchers did not find an expected correlation between tumor localization and LDL binding. $TPPS_4$localizes to tumors in high concentration ratios but binds LDL poorly, 1-2%. This research agues against an LDL mediated mechanism for porphyrin cellular uptake.

36) Nakajima S. and Takemura T. Fundamental studies on the tumor-localizing properties of Photofrin II. Asahikawa, Japan: Asahikawa Medical College, 1992, pp. 1-20.

Nakajima and Takemura induced pancreatic cancer in Syrian golden hamsters with nitrosamine. The researchers then injected the hamsters with 20 mg/kg of HPD (lot 2-01) or Photofrin, original synthetic scheme, lot B-90-120-0045. At different times the hamsters were killed and tumor, liver, lung, kidney, blood homogenized in buffer. Photofrin and HPD were quantified by laser spectrofluorometry.

Fluorescence spectra show that HPD was cleared from plasma slightly faster than Photofrin. This observation is the result of a single experiment and the authors did not calculate pharmacokinetic parameters. Fluorescence spectra also show that tumor tissue retains Photofrin and HPD in concentrations about twice those of liver lung and kidney. Again, the authors did not quantify these results. The authors show only uninterpreted spectra, taken only once at each time point (presumably one animal/drug/time). The authors do establish the lifetime of the excited triplet when Photofrin is irradiated with 400 nm light. The 690 nm phosphorescence decays with a lifetime ($t_{1/e}$) of $8\pm2 \times 10^{-3}$ sec. This result is anticipatably similar to the phosphorescence lifetime of PPIX. Intracellular fluorescence correlates poorly with PDT efficacy, because Photofrin oligomers are not fluorescent. The authors seem to be unaware of this problem.

Interestingly, Nakajima and Takemura show that Photofrin does generate singlet oxygen. They isolated the products of the photo-oxidation reaction between Photofrin and limonene or cholesterol chromatographically. The oxidation of these compounds by singlet oxygen is regio-selective.

38) Bugelski P *et al.* Autoradiographic distribution of hematoporphyrin derivative in normal and tumor tissue of the mouse. *Cancer Res.* 1981; 41:4606-4612.

Bugelski *et al.* implanted tumors s.c. in mice by trochar. They injected the mice with ^3H labeled HPD. ^3H-HPD was uniformly distributed over tissue section of normal stomach, liver spleen and pancreas three hr after i.p. injection. After 24 hours the density of Photofrin in parenchymous areas of these tissues was lower than that in stromal or reticuloendothelial areas. In tumor Photofrin concentrated in pseudo-capsule, stromal, septal and necrotic areas. At 168 hrs Photofrin was found in highest concentration in stromal cells, presumably macrophages. The authors speculate that vascular permeability, lack of adequate lymphatic drainage and nonspecific binding of serum proteins to stromal elements are responsible for the uptake or retention of HPD by tumor tissue. These findings suggest that Photofrin concentrates not in tumor cells, but within attendant white cells.

58) Woodburn KW *et al.* Evaluation of tumour and tissue distribution of porphyrins for use in photodynamic therapy. Br J Cancer. 1992; 65:321-328.

Woodburn *et al.* measured the partition coefficient and tissue localization of 12 synthetic porphyrins and HPD by extraction and fluorescence. HPD localized to tumor more completely than all but one of the synthetic porphyrins. The partition coefficient of HPD decreased exponentially from 5 at pH 6.6 to nearly 0 at pH 7.4. The following table shows the concentration of HPD in tumor and in seven tissues in μg/g (wet) and in blood in μg/ml.

Time	Tumor	brain	skin	muscle	kidney	spleen	liver	lung	blood
6	10.2	0.19	4.31	2.85	20.6	23.7	63.3	17.7	3.00
24	6.2	0.18	4.20	1.17	12.1	25.9	40.0	7.20	1.94

Though HPD was one of the best porphyrins tested, concentrations in tumor are still substantially less than concentrations found in kidney, spleen, liver and lung at both 6 and 24 hours. Notably, the concentra-tion of HPD decreases in tumor at the same rate as in other tissues except brain, skin and spleen. In these tissues the concentration remains nearly constant for 24 hours. The ratio of tumor concentration/brain con-centration remains high, and spleen is not likely to be a target for PDT. Nevertheless, this result suggests that PDT may not discriminate well between normal skin and some tumors. The near constant concentration in skin reemphasizes the danger of skin photo-sensitivity.

59) Baumgartner R *et al.* Pharmacokinetics of fluorescent polyporphyrin Photofrin II in normal rat tissue and rat bladder tumor. *Photochem Photobiol* 1992; 55:569-574.

Baumgartner *et al.* measured the fluorescence due to Photofrin in rat tissues as a function of time *in vivo*. The tissues they studied were abdominal muscle, small intestine, bladder and liver. Photofrin was detected in all tissues from 3 hours to 28 days post injection. The researchers fit their data to a two exponential equation by non-linear regression and calculated the half-lives for Photofrin in these rat tissues. The equation was:

$$F = A[P\exp(-1/t_f) + (1-P)\exp(-1/t_s)]$$

Where A is the initial fluorescence at three hours post injection. P is the fluorescence decay during the fast (distribution) phase and t_f and t_s are the fast and slow time constants. The results of this analysis are shown in the following table.

Organ	A	P	t_f (h)	t_s (h)
Abd. muscle	4.78	0.55	1.32	292.4
Leg muscle	4.57	0.71	2.11	293.3
Small intestine	11.54	0.42	1.80	444.5
Bladder	8.19	0.56	3.61	369.0
Liver	12.75	0.65	43.48	578.0

A and P are in arbitrary units and the time constants are in hours. Liver eliminates Photofrin much more

slowly than the other tissues tested. The half-live for the fast phase of elimination is nearly two days. This study shows that as late as 28 days detectable concentrations of Photofrin remain in tissues. The retention of Photofrin in liver and the high concentration seen in study 59 clearly warn that irradiation of the liver during PDT should be avoided. PDT within the plural or peritoneal cavities could seriously damage major organs, particularly if these organs are accidentally irradiated.

121) Bellnier DA *et al.* Distribution and elimination of Photofrin II in mice. *Photochem Photobiol.* 1989; 50(2);221-228. (this study is the same one as reference 208).

Bellnier *et al* gave ^{14}C-Photofrin to normal and SMT-F tumor baring DBA/2Ha-DD mice, 5 mg/kg i.p. They determined urinary and fecal excretion for 192 hours. They followed plasma concentration for 48 hours after injecting 5 mg/kg i.v. and for 75 days after i.p. injection. They determined tissue distribution after doses of 5 and 27 mg/kg i.p. Radiation recovery was 100 ± 10%.

The results of the excretion analysis are presented in the following table. The authors did not account for the remaining 35% of the radioactivity but tissue concentrations at 15 days suggest that it remains in the animal at 192 hours.

Recovery of radioactivity in urine and feces of tumor free mice

	% of administered dose	
Collection time in hr	Urine	Feces
0-24	2.4	27.1
24-48	1.2	10.4
48-72	0.7	6.0
72-96	0.7	3.8
96-120	0.4	2.7
120-144	0.3	3.6
144-168	0.2	2.8
168-192	0.2	3.0
total	6.2	59.4

Plasma clearance after i.v. administration best fit a tri-exponential with distribution and elimination half-lives of 0.75, 10 and 220 hours. Long term plasma clearance best fit a bi-exponential with elimination half-lives of 220 and 870 hours. Plasma clearance after i.p. administration best fit a bi-exponential with distribution and elimination half-lives of four and 220 hours. The absorption half-life was about one hour. The following charts present these results.

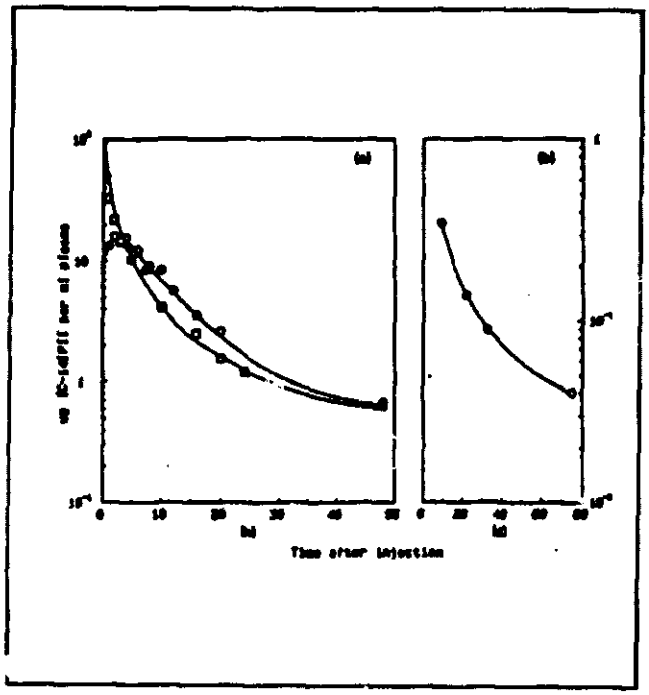


Figure 1. Clearance of ^{14}C-Photofrin from the plasma of mice following i.p. ( ) or i.v. (') administration of 5 mg/kg ^{14}C-Photofrin/kg. Each point is the mean of 3-6 animals; standard deviations did not exceed 30%. Concentration were calculated as if all radioactivity was accounted for by ^{14}C-Photofrin. Curves fitted by eye.

The concentration of Photofrin increase in soft tissues for almost 10 hours, possibly accounting for the 4 hour distribution half-life. Photofrin was eliminated from soft tissues much more slowly than from plasma. The following graphs show the elimination from selected tissues on two time scales.

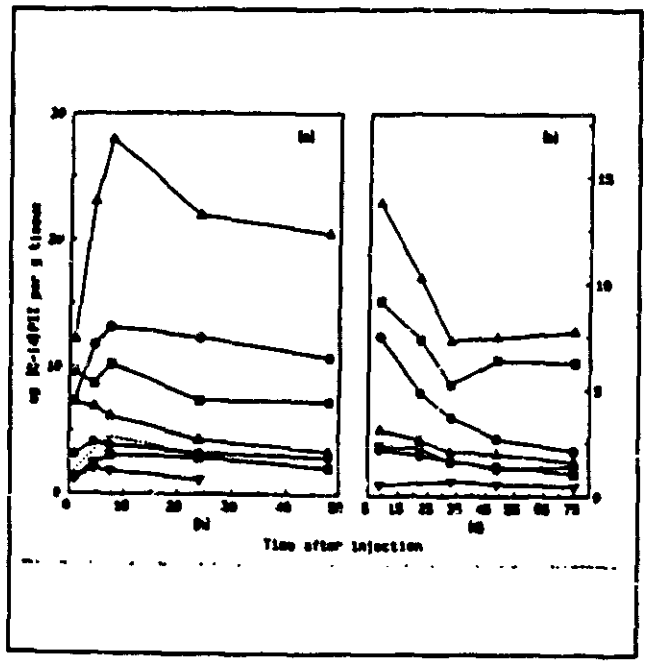


Figure 2. Distribution of radioactivity into mouse tissues. Animals received 5 mg ^{14}C-Photofrin/kg i.p. and were sacrificed at the indicated times following drug administration. Data are the averages of 3-6 animals; standard deviations were < 30%. Concentrations in liver (•), kidney ( ), spleen ( ), lung (□), heart ( ), skin contralateral to tumor ('), muscle (–), and SMT-F tumor (.....) were calculated as if all radioactivity was accounted for by ^{14}C-Photofrin.

Relatively high concentrations of Photofrin remained in liver and spleen past 75 days and Photofrin was detectable in lung, heart, kidney and skin tumor. Table 2 shows concentration in selected tissues after a dose of 27 mg/kg.

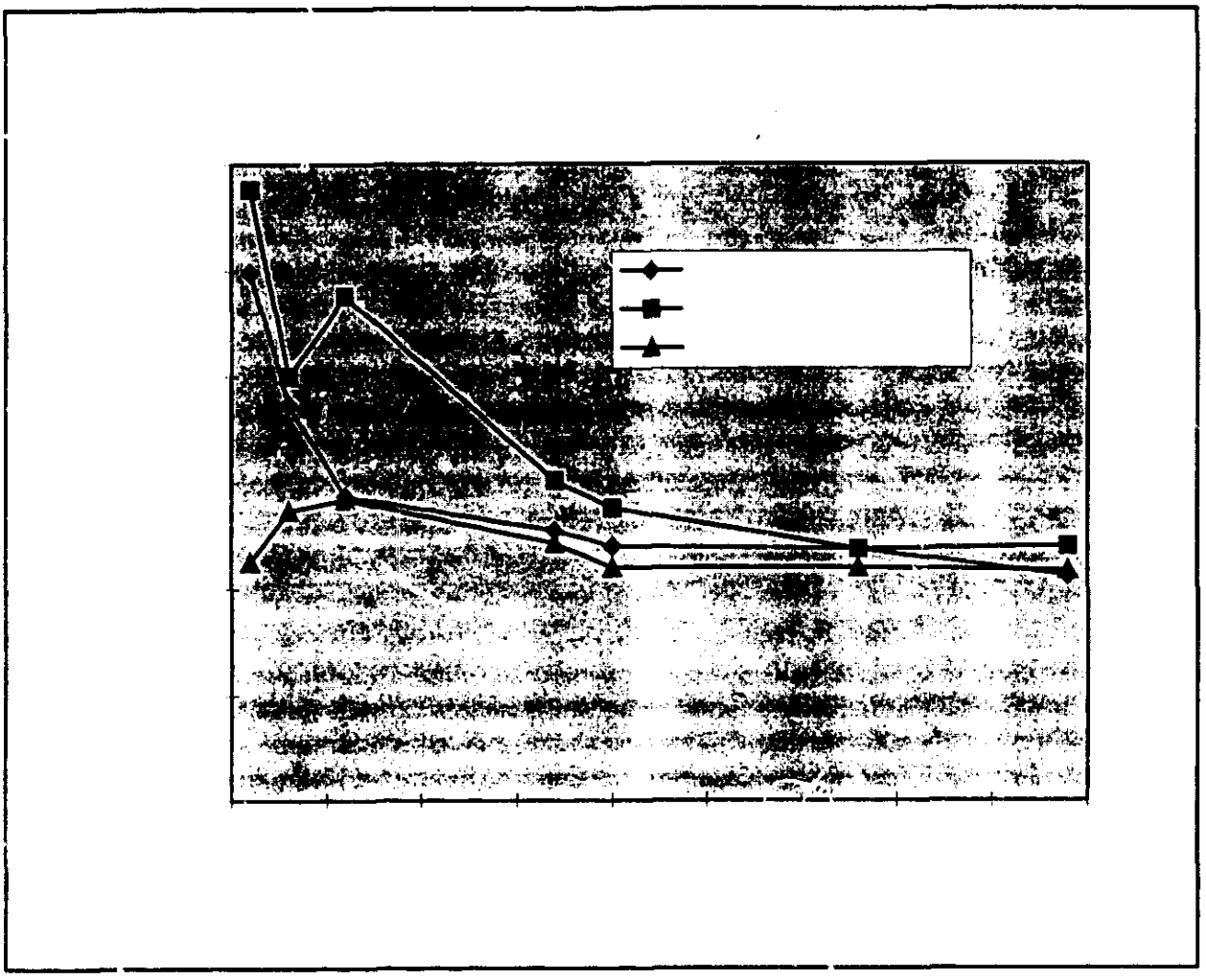
Table 2. Distribution of radioactivity into tissues of mice receiving ^{14}C Photofrin.

Tissue	Time after injection	µg ''CPII /g tissue	s.d.	normalized concentration	n
Liver	24h	109.7	3.7	20.6	4
	8d	72.1		13.5	4
	15d	59.8		11.2	4
Brain	24h	0.84	0.13	0.16	3
Spleen	24h	50.1	0.9	9.39	3
Stomach	24h	30.0	1.1	5.63	3
Pancreas	24h	68.4	1.7	12.8	3
	15d	28.3	1.7	5.31	4
Bone	24h	26.2	4.4	4.93	3
Adrenal gland	24h	103.4		19.4	7
	8d	88.9		16.7	4
	15d	76.0		14.3	4
Urinary bladder	24h	93.6		17.6	3
Plasma	24h	6.47		1.21	3

Concentration was calculated assuming all radioactivity is in the form of the parent compound. Concentrations in the fourth column are normalized to an injected dose of 5 mg/kg for comparison. Average values shown without standard deviations are from pooled tissue samples.

The following figure shows that the concentration of Photofrin within a tumor decreases exponentially with excised tumor weight. Thus large tumors take up less Photofrin than small ones. This is probably because larger tumors are more poorly perfused than small ones. The concentration in skin over tumor de-creases even more rapidly with increased tumor weight. The variation in the concentration in skin contralat-eral to tumor is probably statistically indistinguishable from 0 but the investigators did not do an ANOVA.

The investigators in this study implanted these tumors s.c. Photofrin is selectively retained in skin over the tumor in concentrations greater than the concentration in the tumor. These results and others briefly reviewed by the authors suggest that the therapeutic index ([Photofrin] in tumor divided by the concentration in normal surrounding tissue) is tissue and tumor specific. The most important finding of this research is that over half or administered radioactivity remains in liver and adrenal glands 15 days after dosing. The methods of detection used by these investigators cannot distinguish Photofrin from its many metabolites.



206) Sabben G. *et al.* Time dependence of ^{3}H-Hematoporphyrin derivative distribution in the digestive tract in the rat. In: Andreoni A and Cubeddu R. eds. *Porphyrins in Tumor Phototherapy.* New York, NY: Plenum Press; 1984: 243-245.

Sabben *et al* tritiated HPD by catalytic exchange. They injected this radio-labeled HPD, 10 mg/kg, into male rats. They killed the rats at varying times and counted the radio-label in oxidized tissue samples. The table below shows these results.

[^{3}H-HPD] in different tissues with time µg/g

Detectable radio-label concentration peaked at 4 hr in all tissues.

Tissue	1 hr	sd	4 hr	sd	72 hr	sd
esophagus	2.10	0.23	2.94	0.70	2.01	0.29
fundus	3.16	0.16	2.52	0.15	1.34	0.11
antrum	3.05	0.18	5.25	0.39	2.36	0.21
small intestine	6.28	0.46	8.10	0.56	4.53	0.54
colon	2.27	0.13	2.40	0.26	1.76	0.10
lung			185			
liver			183			
spleen			119			
kidney			23			

Sabben *et al.* note briefly that most of the radioactivity associated with the liver is found in the Kupffer cells. In the lung they found most of the label associated with the macrophages. These findings are consistent with the hypothesis that the Photofrin causes a general immune stimulation. Immune cells respond to clean up the compound bound to membranes throughout the body.

This research shows that concentrations of Photofrin in normal esophagus are significantly lower than concentrations found in highly metabolic tissues such as lung, liver and kidney.

207) Pantelides M *et al.* A comparison of serum kinetics and tissues distribution of Photofrin II following intravenous and intraperitoneal injection in the mouse. *Photochem Photobiol.* 1989: 49(1)67-70.

Pantelides *et al* studied the tissue distribution of Photofrin with time. They determined the Photofrin from the fluorescence of tissue extracts. Their work is consistent with that of other researchers in showing high and persistent concentrations of Photofrin in liver, spleen, and kidney. Peak concentrations in these organs were about twice as high when these researchers administered Photofrin, 10 mg/kg, to mice i.v. as when they gave it i.p. Oligomeric Photofrin does not fluoresce, so Pantelides *et al* extracted the tissue by a second technique to quantify all the porphyrin in the tissues. They heated the acidic extract to hydrolyze the linked porphyrin monomers. In all cases this method increased the fluorescence signal by at least a factor of four. The authors noted that in all organs, the ratio of fluorescence from heat hydrolysis to that from simple extraction was higher when they gave Photofrin i.v. The following table shows this result.

Relative increase in fluorescence ratios following heat hydrolysis
(data pooled for all tissues other than serum).

Time	i.p.	sd	i.v.	sd	sd
3	4	0.7	7.2	0.4	
24	5.5	0.5	6.5	0.6	<0.05
48	4.9	0.8	7	0.2	
72	4.7	0.7	5.2	0.5	0.1

Isolated serum showed thi.. selective absor,'tion within 10 min after injection. This result implies that tissues absorb more Photofrin oligomer, the photoactive compounds, when Photofrin is injected i.v. Probably much of Photofrin oligomer binds within the peritoneum, thus less is available to diffuse into the circulation.

208) Belliner DA, *et al.* Distribution and elimination of Photofrin II in mice. *Photochem Photobiol.* 1989;50(2):221-228. See reference 121.

211) Hara *et al.* Distribution of hematoporphyrin derivative in normal and malignant tissue. *Jpn J Exp Med.* 1988; **58**(3):139-143.

Hara *et al.* injected a rabbit with ^{14}C-glycine for four days. They collected the blood and synthesized HPD by the standard method (Gomer and Dougherty 1979, *Cancer Res.* **39**:146). They injected this labelled HPD into nude mice with implanted QC 90 small cell carcinoma of the lung. They killed the mice and isolated tissues at different times, then counted the radioactivity in the tissue. Their results are consistent with that of other researchers in showing high concentrations of Photofrin in highly metabolic tissues. These high concentrations persist for more than four days. Notably, like other researchers, Hara *et al.* found that concentrations in this particular tumor were not higher than those found in some normal tissue.

Tissue and serum distribution of ^{14}C-HPD in nude mice at various times following injection.
^{14}C-HPD (dpm) per 100 mg tissue

time	serum	tumor	sd	skin	sd	musclee	sd	kidney	sd	liver	sd
days											
1	24	144	9	95	26	35	7	228	59	338	97
2	15	138	12	80	25	35	5	199	72	424	119
3	21	142	15	97	13	38	5	210	45	286	78
4	14	128	27	104	22	35	9	157	47	265	85
7	13	71	11	70	11	35	5	128	32	231	46

time	spleen	sd	heart	sd	lung	sd	stomach	sd
days								
1	156	27	192	28	231	68	130	42
2	189	37	194	73	170	65	103	25
3	174	36	167	44	150	31	175	39
4	180	30	156	39	160	42	130	38
7	109	29	151	41	107	10	92	23

212) Kaye AH *et al.* Uptake and retention of hematoporphyrin derivative in an in vivo/in vitro model of cerebral glioma. *Neurosurgery.* 1985;17:883-890.

Kaye *et al* implanted C6 glioma tumor lines into rats brains. They detected the presence of injected HPD by the direct fluorescence of tissue sections. HPD caused seizures when the researchers administered it intra-carotid but tumors took up the highest concentrations of HPD. When they injected HPD intra-thecally the tumors took up little HPD. When they injected HPD i.v. or i.p., HPD was uniformly distributed through-out the tumor within six hours. They observed fluorescence in normal brain tissue only in areas outside the BBB. The authors conclude that HPD does not cross the BBB and that C6 glioma takes up HPD in far greater concentrations than normal brain.

213) Carpanini BA *et al.* Uptake and localization of hematoporphyrin derivative in normal rat liver. *Biochem Pharmacol.* 1987; 36;(17):2759-2764.

Carpanini *et al.* established that after an i.p. injection, HPD initially localized to the cytosol of normal rat liver cells. Subcellular fractionation showed that at 24 hours most HPD was within the lysosomes. Also, within 24 hours fluorescence microscopy localized HPD predominantly in Kupffer cells.

218) Jones K. Pilot tissue distribution of ^{14}C-Photofrin II and/or its metabolites in male rats. Protocol reference No. 0687/05PF: 1-38, (1987) Ortho Pharmaceutical (Canada) Ltd. Don Mills, Ontario.

Jones gave ^{14}C-Photofrin, 2.5 mg/kg i.v., to four Sprague Dawley rats. He killed the rats at varying times and counted the radio-label in tissues and excreta. He found 42% or the radio-label in the feces and only 8% in the urine over a 7 day course. Again the highest concentrations of radio-label were found in the liver, about 28% of the total dose after 24 hrs. The concentration of radio-label fell by only $^1/_3$over 7 days in liver, spleen, kidney and most other tissues. Nevertheless, the radio-label found in the blood on day seven was only one tenth the amount found on day one.

219) Bjorkman DJ *et al.* Photofrin II localization in rat cecum. *Lasers Surg Med.* 1989; 9:282-289.

Bjorkman *et al* gave Photofrin to Sprague Dawley rats, 5 mg/kg i.v. They determined the concentration of Photofrin in segments of the rat GI by direct fluorescence. They found that the concentrations of Photofrin localized to the cecum were about 40% greater than that localized to the transverse, descending or sigmoid colon or the rectum. The authors do not speculate on the mechanism responsible for this difference. Nevertheless, this localization is probably due to the higher concentration of porphyrins in the compacting and dehydrating fecal material found in the cecum.

226) Ma LW, *et al.* Effects of light exposure on the uptake of Photofrin II in tumors and normal tissues. *Int J Cancer.* 1992;52:120-123.

Ma *et al.* implanted CaDx mammary carcinoma cells in both flanks of mice. When the tumors reached 85 to 100 mm^3 they injected the mice with 20 mg/kg Photofrin i.p. 1.5 hr later they irradiated the tumor on one side with different energies of laser light, 630 nm. The tumor on the contralateral side served as control. The investigators chose to irradiate at 1.5 hr post dosing because this is when Photofrin reached its peak concentration in the mouse blood. At 24, 48, 72, and 96 hr post dosing they killed groups of 6 mice and determined the concentration of Photofrin in tumor and surrounding tissue by fluorescence emission. The following tables present the major results of this work for the mice killed 24 hours post dosing.

Effect of light exposure in small doses on the concentration of Photofrin II in tumor.

Dose	Control	s.d.	Light	s.d.	p
J/cm^2	µg/g tissue		µg/g tissue		
12.5	10.67	2.18	10.33	2.25	>.05
25	10.19	0.87	19.06	2.09	<0.01
50	10.61	1.89	17.27	1.14	<0.05
75	11.22	1.19	18.96	1.64	<0.05

Effect of light exposure in small doses on the concentration of Photofrin II in skin.

Dose	Control	s.d.	Light	s.d.	p
J/cm^2	µg/g tissue		µg/g tissue		
12.5	6.22	1.18	6.43	0.6	>.05
25	6.65	1.47	8.79	1.59	>.05
50	5.88	1.01	6.98	1.26	>.05
75	6.73	1.49	8.57	1.75	>.05

Effect of light exposure in small doses on the concentration of Photofrin II in muscle.

Dose	Control	s.d.	Light	s.d.	p
J/cm^2	µg/g tissue		µg/g tissue		
12.5	6.1	1.48	5.89	1.04	>.05
25	6.86	0.35	6.07	1.23	>.05
50	6.17	0.44	5.14	0.73	>.05
75	6.23	0.38	5.56	0.49	>.05

Irradiation with 630 nm light caused tumor to take up nearly twice as much Photofrin compared to unirradiated tumors. Irradiation did not significantly increase the uptake of Photofrin in skin or muscle adjacent to the tumors. The authors did not compare the values by ANOVA so the true level of significance is undetermined. Nevertheless the trend to increased concentrations in tumor is clear. The concentration of Photofrin increases sharply between 12.5 and 25 J/cm^2 then stays relatively constant. Photofrin was cleared from irradiated and non-irradiated tissue at about the same rate. The authors postulate that this increase in concentration is due to a light induced decrease in pH in the tumor cells. They suggest that the light causes vascular damage which results in local hypoxia and thus decreased pH. The more normal vasculature of normal tissue is not significantly effected by these low doses of light.

ADME Summary

Many investigators have examined the absorption, distribution and elimination of Photofrin or HPD. These studies usually determine the concentration of Photofrin in tissues by direct fluorescence, extraction and fluorescence, HPLC or by radio-labeling. None of these techniques can accurately determine the concentration of photoactive Photofrin oligomer inside a tissue, the blood or a cell.

The oligomer does not fluoresce as strongly as monomer or aggregate. Thus, fluorescence techniques are better measures of the concentration of monomer and porphyrin aggregate. Cells absorb monomer and aggregate by different mechanisms and at different rates than oligomer. These chemicals do not bind to membranes as strongly as oligomer. Pure monomers are not photoactive, probably because cells exclude them and because they cannot form singlet oxygen. A portion of the oligomer is hydrolyzed to fluorescent monomer inside the cell. Acidic extraction can hydrolyze Photofrin, giving a better measure of true oligomer absorption. Only one study has used this technique. This study (207) showed that tissues absorb more oligomer when Photofrin is given i.v. then when it is given i.p. This is probably because less Photofrin is available systemically, much of it remains in the peritoneum.

Radio-labeling is nonspecific since Photofrin is not synthesized *de novo*. Labeling reactions affect monomer, aggregate and oligomer. Thus, it is difficult to correlate total radioactivity in the cell with the concentration of photoactive oligomer or with efficacy. Oligomer is hydrolyzed to monomer or smaller products that are still radio-labeled. Thus, the elimination of radioactivity under-estimates the elimination of photoactive oligomer.

Photofrin injected i.v. is eliminated from the plasma quickly, the distribution half-life is less than 1 hour. Elimination from tissues is more protracted, Bellnier *et al.* (121) estimated half-lives of 10, 220 and 870 hr in the mouse using ^{14}C-Photofrin. In an HPLC study (223) a two exponential model determined an elimination half-life of 46 hr in the dog. Both rat and dog eliminate porphyrin monomers much more quickly than Photofrin, $t_{1/2}b < 1$ hr. In studies with both rat and dog the Photofrin AUC increased linearly with dose to 10 mg/kg.

Injected Photofrin distributes in greatest concentrations to highly vascular tissues with large num-bers of resident immune cells such as liver, spleen, kidney and lung. This probably occurs because the monocytes, PMNs, or Kupffer cells scavenge the photofrin from the blood to eliminate it. Tumors frequent-ly contain large populations of white cells. The accumulation of Photofrin in white cells may also explain it selective concentration in some tumors. Concentrations in liver can be more than 30 times greater than con-centrations in blood. The elimination of Photofrin from liver is protracted and accounts for the longer half-life terms given above. In all the studies I have seen, the concentrations of Photofrin in these normal tissues were higher than the concentrations in implanted tumors. Concentrations of Photofrin found in muscle, skin, colon and esophagus, most epithelium and brain are consistently 10 to 1000 fold less than concentrations in vascular organs. In blood 70% of injected Photofrin binds to HDL, 14 % binds to serum albumin.

Jones (218) gave radio-labeled photofrin to rats. He found 42% of the radio-label in the feces by day 7 and only 8% in the urine. This is consistent with the slow elimination of Photofrin. The enzymatic destruction of Photofrin oligomer is poorly characterized. After dosing, lysosomes take up Photofrin in high concentrations, here degradive enzymes and superoxide ion probably destroy it. Aroclor 1254 induced S9 increases the toxicity of Photofrin PDT in mutagenicity studies. This result implies that Cytochrome P-450 1A1 activates Photofrin or some Photofrin breakdown product to a more potent toxin. This toxic metabolite has not been described.

Overall Summary and Evaluation

Photofrin is clearly toxic at doses greater than 300 mg/m^2. Fortunately this dose is at least three times greater than the effective clinical dose. Photofrin causes splenomegaly, hepatomegaly and lymph node swelling. It can cause necrosis and hemorrhage in papillary muscles of the heart. It causes ischemic necrosis in the kidneys. Photofrin break down products and hemosiderin deposit in cells that take up large concentrations.

Once weekly exposure to 10 mg/kg of Photofrin for 13 weeks caused anorexia, weight loss and increased organ weights in ovaries and testes of rats. This exposure caused increased weights in adrenals, thyroid and prostate in males and thymus in females. Sub-acute exposure caused changes in rat epididymis and seminal vesicles. Photofrin does not cross the intact blood brain barrier, but does concentrate in brain tumors where the BBB is disrupted. No one has determined whether Photofrin crosses the placental barrier. Photofrin causes a general immune stimulation. Immune cells respond to clean up the compound bound to membranes throughout the body. This immune stimulation probably accounts for the mild fever observed in 23 of 74 patients receiving photofrin for treatment of esophageal cancer.

"Aged" or improperly stored Photofrin causes slightly less mortality in mice and rats and causes fewer toxic symptoms. The spectrum of toxicities is similar to freshly made Photofrin. Similarly, the spectrum of toxicities caused by the original frozen formulation was similar to that caused by a lyophilized formulation in the dog. Both of these studies used Photofrin made by synthetic scheme I.

Photosensitivity is the most well understood toxicity of Photofrin. Tissues exposed to light after Photofrin administration suffer edema and erythema. Longer term or high intensity exposure causes edema and burns with scabbing. After a single dose of Photofrin, high intensity light can damage the retina irreparably. Light exposure causes destruction of RBCs circulating under the exposed area, Hct and Hbg decrease. This photo-damage can progress to cause thrombosis and shock resulting in death. Damage to the blood is dependant on the time, intensity and area of exposure.

Photofrin clears from the blood within hours, but it persists in many tissues for days. Well perfused tissues with large complements of immune cells such as liver, spleen, lung and kidney accumulate Photofrin in the highest concentrations. These concentrations are higher than those within implanted tumors. Thus tumors within these tissues are poor candidates for photodynamic therapy. The high Photofrin concentrations in these organs also warn that open peritoneal or plural cavities are dangerous places for PDT.

Concentrations of Photofrin found in muscle, skin, colon and esophagus, most epithelium and brain are consistently 3 to 100 fold less than those in the organs listed above. Concentrations in these tissues are usually less than half the concentration in implanted tumor, making these tissues better targets for PDT. High and low concentration tissues clear Photofrin at about the same rate, about half disappears in seven days. However, skin accumulates ^{14}C-HPD in concentrations less than one third those found in liver, but can clear only half as much proportionately with time. Skin probably clears Photofrin by photo-bleaching and sloughing. Thus pharmacokinetic parameters underestimate the time course and severity of skin photosensitivity. Direct fluorescence does not accurately quantify Photofrin concentrations in tissues, because Photofrin aggregates and oligomers have low fluorescence quantum yields.

Glucocorticoids given to mice bearing Lewis lung carcinoma after HPD-PDT increase the time required for tumors to regrow. Methylprednisolone acetate, 0.6 mg/kg nearly doubled the efficacy of HPD-PDT. The acetate was more effective than the succinate. Increasing the dose beyond an optimum decreased the efficacy of PDT. Prophylactic administration of methylprednisolone acetate decreased the efficacy of HPD-PDT.

Glucose, 3 g/kg, given to mice bearing tumors at intervals to 16 hr after Photofrin dosing and immediately after irradiation at 6 g/kg, doubled the tumor response. Hyperglycemia increases the intracellular pH of tumors. Increased pH probably trap Photofrin as an anion inside the cell. Hyperglycemia does not increase the uptake of Photofrin by normal tissues. Hyperglycemia also decreases tumor perfusion. Stopping glucose administration 32 hours before irradiation allows the tumors to re-oxygenate.

Drugs such as SQ-29548, R68070 (thromboxane receptor agonist and thromboxane synthetase inhibitor respectively) and flunarizine (inhibits platelet shape change) markedly reduced tumor cures. These drugs reduce or prevent vascular constriction after Photofrin-PDT. SQ-29548 and R68070, but not flunarizine, inhibit the PDT associated increase in vascular permeability. Paradoxically, aspirin does not reduce tumor response, so changes in vascular permeability may not be central to the PDT mechanism. Studies of the time course of the histopathology caused by PDT show that much of the damage caused by PDT results from vascular constriction, the aggregation of platelets, and clotting. Many tumor cells die from ischemia, secondary to coagulation. Other drugs that diminish or prolong clotting may decrease the efficacy of Photofrin-PDT. The complete mechanism of this damage remains to be defined.

Allopurinol, a xanthine oxidase inhibitor, and Ca^{++}channel blockers such as verapamil can decrease the effectiveness of Photofrin-PDT by as much as 90% in animal models. These compounds decrease the amount of superoxide generated by xanthine oxidase during Photofrin-PDT.

Hypoxic radio-sensitizers, such as misonidazole, given 15 min before Photofrin increase tumor response in rats. This increase is synergistic, 38% more than additive measured by tumor growth delay. Misonidazole given 30 min after irradiation delays tumor growth 48% more than additive. Hyperthermia has a similar effect. Intracellular thiols scavenge radicals. Misonidazole may increase tumor damage by depleting intracellular thiols.

In standard GLP studies Photofrin appeared to cause no genotoxicity, particularly without irradiation. Photofrin plus light, with or without S9 activation did not cause reversion mutations at the Salmonella/histidine locus of five tested bacterial strains. The significance of these results in non-mammalian cells is questionable because it is unlikely that Photofrin crosses the bacterial cell wall. Photofrin plus light with or without S9 activation did not cause mutations at the HGPRT locus of CHO cells. In another study Photofrin did not cause chromosomal aberrations in CHO cells. In a GLP study of sister chromatid exchange in CHO cells, Photofrin plus light caused increases in aberrations statistically greater than controls, but these increases were less than 1.5 fold. Nevertheless, these studies were seriously flawed. In each of the three, mutations were determined at single Photofrin concentrations and these concentrations were not cytotoxic to the requisite 70 to 90% of the cells. In experiments where the cells were irradiated, the Photofrin was in solution over the cells, so much of the light was absorbed before it reached the cells. These studies provide little useful information about the genotoxicity of Photofrin. In a fifth GLP study, Photofrin did not cause chromosomal aberrations in a mouse micronucleus test.

In some non-standard assays the increase in mutations has been greater than two fold, particularly in sister chromatid exchange experiments where it is as high as three fold. Photofrin plus light caused an increase in the number of thymidine kinase mutants in heterozygous mouse lymphoma cell lines. This genotoxicity increased non-linearly with light density to 100 kJ/m^2. The mutation rate was not as great as that caused by X-radiation. Other non-GLP assays have shown an increase in chromosomal aberrations, but none greater than three fold and usually only at high concentrations and light energies. Photofrin does not cross the nuclear membrane, but Photofrin-PDT can damage DNA. Radical chain reaction initiated outside the nucleus can propagate across the membrane and cause strand breaks. This damage is different from X-ray damage and is repaired by different mechanisms.

Conditions that produce this DNA damage are usually severely cytotoxic. This body of information suggests that Photofrin-PDT may be genotoxic. However, Photofrin-PDT appears to be substantially less genotoxic than some other cancer chemotherapies.

Photofrin given to parent rats (i.v. to 4.0 mg/kg/d or 23.6 mg/m^2 for females and males) before conception and through day 7 of pregnancy for the females, caused no gross developmental abnormalities in the offspring. These doses caused no changes in fetal mortality, sex ratio or body weight. These daily doses of Photofrin did cause hypertrophy of the ovaries and testes in the parents and as much as 20% decrease in body weight. In studies where Photofrin was given to rat dams during fetal organogenesis (i.v. 4 and 8 mg/kg/d, days 7 to 17 post conception) the drug caused fetal abnormalities. These abnormalities included increased resorptions, decreased litter size, reduced fetal weight and delayed ossification. Other changes were minor, there were no major malformations or developmental changes. These abnormalities can be attributed to maternal toxicity, i.e. weight loss. When Photofrin was given to rats during late pregnancy and lactation (i.v. 0.5 to 4 mg/kg/d, day 17 post conception through day 21 postpartum) the highest dose caused a reversible 15% decrease in growth in the f_1 generation by week two postpartum. The NOEL for f_0 dams was 0.5 mg/kg/d, for f_1 generation 2 mg/kg/d. No toxic effects were seen in the f_2 generation. Photofrin caused similar minor gestational abnormalities in rabbits. These daily doses are less than the single clinical dose for human patients (2 mg/kg or 74 mg/m^2) on a mg/m^2 basis.

For PDT to be effective tumors should concentrate significantly more Photofrin than surrounding normal tissue. Experiments determining the Photofrin concentration in tumor verses the Photofrin concentration in normal surrounding tissue show that this ratio is tumor specific. Photofrin uptake by particular tumors is difficult to predict prior to therapy. Verapamil reduces the clearance of Photofrin from tumor cells *in vitro*. This slower clearance implies that Photofrin is a substrate for P-glycoprotein (MDR). Thus, tumors that overexpress P-glycoprotein may be resistant to Photofrin-PDT. Photofrin-PDT resistance has been induced in vitro. Experiments to compared the exclusion of Photofrin by tumor cells expressing p-glycoprotein with that of normal parent cell lines have not been done.

The concentrations of Photofrin in normal esophagus are significantly lower than concentrations found in highly metabolic tissues such as lung, liver and kidney. Esophageal carcinoma may be especially suited to Photofrin-PDT.

The sponsors have submitted an impressive amount of pre-clinical data describing the safety and efficacy of Photofrin and Photofrin-PDT. Nevertheless, they have submitted no studies describing the pharmacology and toxicology of the Photofrin formulation now used clinically. HPD clears from plasma faster than Photofrin. It is also less toxic and less effective than Photofrin. Some gel filtration purified fractions of Photofrin are more toxic than the parent mixture. In a published report (176) the authors include a footnote that says "a batch of PFII (Photofrin from QLT)(manufactured 4/89, MRWO No. P89-0089) was found to be very cytotoxic when dissolved in physiological saline, but not when dissolved in 5% dextrose. The toxicity was observed with or without light irradiation, but the increase in phototoxicity could not be entirely accounted for by the increased dark toxicity." The authors did not use this batch for their experiments. This batch of Photofrin was not used in any studies submitted to the NDA where I could identify the batch number. This footnote suggests some non-uniformity in the Photofrin manufacture process. Thus, it is reasonable to expect that the Photofrin formulation now used clinically may be toxicologically different from its well studied predecessors. This toxicological difference is unlikely to be clinically significant if the new Photofrin formulation is simply a mixture of the same compounds in different ratios. However, the chemical composition of this new formulation remains undetermined. Given this uncertainty, the sponsor should conduct a bridging toxicology study with the Photofrin formulation that will be used clinically.

Labeling

1) In the section"Pharmacology" the seventh sentence should be modified in accord with the following:

Intracellular PHOTOFRIN-PDT damage results from radical reactions. Radical initiation may occur after PHOTOFRIN absorbs light to form a porphyrin excited state. Spin transfer from PHOTOFRIN to molecular oxygen may then generate singlet oxygen. Subsequent radical reactions can form superoxide and hydroxyl radicals.

2) In the section "Drug Interactions" the second paragraph should be modified in accord with the following:

PHOTOFRIN-PDT causes direct intracellular damage by initiating radical chain reactions. These reactions propagate through the cell and are particularly destructive to intracellular membranes and mitochondria. Nevertheless, much of the tissue damage caused by PDT results from ischemia. This ischemia is secondary to vasoconstriction, platelet activation and aggregation and clotting. Research in animals and in cell culture has shown that many drugs may influence the efficacy of PDT.

Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulfoxide, β-carotene, ethanol, formate and mannitol decrease PDT activity. Cells ischemic prior to irradiation are protected from PDT activity. Xanthine oxidase inhibitors, e.g. allopurinol, and calcium channel blockers, e.g. verapamil, decrease PDT damage to normal tissue by a complex mechanism that decreases the production of radicals. The influence of calcium channel blockers on PDT efficacy is probably tumor specific. Indomethacin, a prostaglandin synthesis inhibitor, added to cells in culture before PDT protects against direct damage. Some drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g. thromboxane A_2 inhibitors, decrease the efficacy of PDT. Glucocorticoid hormones given before or concomitant with PDT decreased the efficacy of the treatment.

2) The section "Carcinogenesis, Mutagenesis, Impairment of Fertility" should be modified in accord with the following:

No long term studies have been conducted to evaluate the carcinogenic potential of PHOTOFRIN. *In vitro*, PHOTOFRIN-PDT, with or without S9 activation, did not cause mutations in the Ames test. Nor did it cause chromosome aberrations or mutations (HGPRT locus) in Chinese hamster ovary (CHO) cells. PHOTOFRIN caused <2 fold, but significant, increases in sister chromatid exchange in CHO cells irradiated with visible light and a 3 fold increase in Chinese hamster lung fibroblasts irradiated with near UV light. PHOTOFRIN-PDT caused an increase in thymidine kinase mutants and DNA-protein cross-links in mouse L5178Y cells, but not mouse LYR83 cells. PHOTOFRIN-PDT caused a light-dose dependant increase in DNA-strand breaks in a malignant human cervical carcinoma cells, but not in normal cells. The mutagenicity of PHOTOFRIN without light has not been adequately determined. *In vivo*, PHOTOFRIN did not cause chromosomal aberrations in the mouse micronucleus test.

PHOTOFRIN given to male and female rats intravenously, at 4 mg/kg/d (0.32 times the clinical dose on a mg/m^2basis) before conception and through day 7 of pregnancy caused no impairment of fertility, but did cause hypertrophy of the ovaries, and testes and decreased body weight in the parent rats.

2) The section "Pregnancy" should be modified in accord with the following:

PHOTOFRIN given to rat dams during fetal organogenesis intravenously at 8 mg/kg/d (0.64 times the clinical dose on a mg/m^2basis) caused no major malformations or developmental changes. This dose caused maternal and fetal toxicity resulting in increased resorptions, delayed ossification, decreased litter size, and reduced fetal weight. PHOTOFRIN caused no major malformations when given to rabbits intravenously during organogenesis at 8 mg/kg/d (1.5 times the clinical dose on a mg/m^2 basis).

PHOTOFRIN given to rats during late pregnancy through lactation intravenously at 4 mg/kg/d (0.32 times the clinical dose on a mg/m^2basis), caused a reversible decrease in growth of offspring.

Recommendation:

1) The pharmacology/toxicology section of this NDA is adequate for approval.

2) The sponsor has submitted no pre-clinical information describing the toxicity and histopathology of the Photofrin formulation currently used clinically. The sponsor should conduct a preclinical study describing the toxicity of the formulation of Photofrin currently used clinically. This study should span doses that are clearly toxic and include one dose that causes some mortality. The study should include a recovery period of at least 8 days and should describe the gross pathology and histopathology that results. This study may be done during phase IV of development.

Suggestions

1) The sponsor may wish to re-test the genotoxicity Photofrin. Data suggests that Photofrin with and without light may cause significant sister chromatid exchange or HGPRT mutations in Chinese Hamster Ovary cells. GLP genotoxicity studies should be conducted at Photofrin concentrations that cause significant cytotoxicity (70 to 90% cell death for the maximum dose). Such studies should be done with at least three and preferably five concentrations. The cells should be exposed to Photofrin for five to eight hours in the dark. The Photofrin solution then should be washed from the cells before irradiation

so that the cells are not shielded by the Photofrin absorbance. Sister chromatid exchange or HGPRT mutation should also be determined in non-irradiated cells at cytotoxic concentrations.

W. David McGuinn, Jr., Ph.D.

March 15, 1995

completed August 12, 1994
revised December 15, 1994

cc:
Original NDA
HFD-150/Division File
HFD-150/W D McGuinn
HFD-150/J J DeGeorge
HFD-150/P Zimmerman--received 4/17/95
HFD-150/G Williams

Proposed pharm/tox labeling changes for PHOTOFRIN ***DRAFT***

iteration *V*

Please Comment

1) In the section"Pharmacology" the seventh sentence should be modified in accord with the following:

Intracellular PHOTOFRIN-PDT damage results from radical reactions. Radical initiation may occur after PHOTOFRIN absorbs light to form a porphyrin excited state. Spin transfer from PHOTOFRIN to molecular oxygen may then generate singlet oxygen. Subsequent radical reactions can form superoxide and hydroxyl radicals

2) In the section "Drug Interactions" the second paragraph should be modified in accord with the following:

PHOTOFRIN-PDT causes direct intracellular damage by initiating radical chain reactions. These reactions propagate through the cell and are particularly destructive to intracellular membranes and mitochondria. Nevertheless, much of the tissue damage caused by PDT results from ischemia. This ischemia is secondary to vasoconstriction, platelet activation and aggregation and clotting. Research in animals and in cell culture has shown that many drugs may influence the efficacy of PDT.

Compounds that quench active oxygen species or scavenge radicals, such as dimethyl sulfoxide, β-carotene, ethanol, formate and mannitol decrease PDT activity. Cells ischemic prior to irradiation are protected from PDT activity. Xanthine oxidase inhibitors, e.g. allopurinol, and calcium channel blockers, e.g. verapamil, decrease PDT damage to normal tissue by a complex mechanism that decreases the production of radicals. The influence of calcium channel blockers on PDT efficacy is probably tumor specific. Indomethacin, a prostaglandin synthesis inhibitor, added to cells in culture before PDT protects against direct damage. Some drugs that decrease clotting, vasoconstriction or platelet aggregation, e.g thromboxane A_2 inhibitors, decrease the efficacy of PDT. Glucocorticoid hormones given before or concomitant with PDT decreased the efficacy of the treatment.

2) The section "Carcinogenesis, Mutagenesis, Impairment of Fertility" should be modified in accord with the following:

No long term studies have been conducted to evaluate the carcinogenic potential of PHOTOFRIN. *In vitro*, PHOTOFRIN-PDT, with or without S9 activation, did not cause mutations in the Ames test. Nor did it cause chromosome aberrations or mutations (HGPRT locus) in Chinese hamster ovary (CHO) cells. PHOTOFRIN caused <2 fold, but significant, increases in sister chromatid exchange in CHO cells irradiated with visible light and a 3 fold increase in Chinese hamster lung fibroblasts irradiated with near UV light. PHOTOFRIN-PDT caused an increase in thymidine kinase mutants and DNA-protein cross-links in mouse L5178Y cells, but not mouse LYR83 cells. PHOTOFRIN-PDT caused a light-dose dependant increase in DNA-strand breaks in a malignant human cervical carcinoma cells, but not in normal cells. The mutagenicity of PHOTOFRIN without light has not been adequately determined. *In vivo*, PHOTOFRIN did not cause chromosomal aberrations in the mouse micronucleus test.

PHOTOFRIN given to male and female rats intravenously, at 4 mg/kg/d (0.32 times the clinical dose on a mg/m^2 basis) before conception and through day 7 of pregnancy caused no impairment of fertility, but did cause hypertrophy of the ovaries, and testes and decreased body weight in the parent rats.

2) The section "Pregnancy" should be modified to read:

PHOTOFRIN given to rat dams during fetal organogenesis intravenously at 8 mg/kg/d (0.64 times the clinical dose on a mg/m^2 basis) caused no major malformations or developmental changes. This dose caused maternal and fetal toxicity resulting in increased resorptions, delayed ossification, decreased litter size, and reduced fetal weight. PHOTOFRIN caused no major malformations when given to rabbits intravenously during organogenesis at 8 mg/kg/d (1.5 times the clinical dose on a mg/m^2 basis).

PHOTOFRIN given to rats during late pregnancy through lactation intravenously at 4 mg/kg/d (0.32 times the clinical dose on a mg/m^2 basis), caused a reversible decrease in growth of offspring.

W. David McGuinn, Jr., Ph. D.

cc:
Orig NDA 20451
DIV file
HFD-150/D. McGuinn
1 P Zimmerman
1 J DeGeorge
1 C Williams

3/8/95

3/20/95

Chem

P Zimmerman

DEC 16 1995

Division of Oncology Drug Products
HFD-150
Review of Chemistry, Manufacturing and Controls

NDA #: 20-451 **Chemistry Review #:** 03 **Review Date:** 13-Dec-1995

Submission Type	Document Date	CDER Date	Assigned Date
Amendment (AZ)	04-Dec-1995	06-Dec-1995	06-Dec-1995

Name & Address of Applicant QLT PhotoTherapeutics, Inc.
520 West 6th Avenue, Vancouver
British Columbia, Canada V5z 4H5

Drug Product Name:

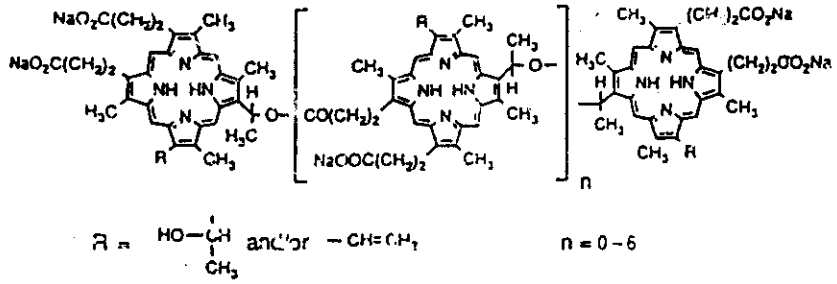
Proprietary:	Photofrin for Injection
Nonproprietary/USAN:	Porfimer Sodium for Injection
Code Name/Number:	CL 184,116
Chem. Type/Ther. Class:	1P

ANDA Suitability Petition/DESI/Patent Status: N/A

Pharmalogical Category/Indication:	Reduction of obstruction and palliation of dysphagia in patients with completely or partially obstructing esophageal cancer
Dosage Form:	Lyophilized Sterile Powder for Injection
Strength:	75 mg/vial
Route of Administration:	Intravenous Infusion

Dispensed: _x_ Rx ___ OTC

Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:



Supporting Documents: IND 25,064

Related Documents (if applicable):

DMF	DMF
MAF	DMF
DMF	DMF
DMF	DMF

Comments:

This amendment provides responses to the Agency's Approvable Letter dated July 13, 1995. Most of the deficiencies cited in the Approvable Letter were discussed and resolved in the October 31, 1995 meeting between the Agency and the firm (See Minutes of October 31, 1995 Meeting). Our major concern is that the current level of control and characterization of the drug product should be improved to assure the identity, strength, purity and quality, as well as the lot-to-lot uniformity of the drug product. The applicant has made commitment to develop a capillary electrophoresis assay which is capable of fingerprinting the photophyrin oligomeric mixture postapproval, for the analysis of retention samples and subsequent setting of drug product specifications for release and shelf - life testing.

We recognize the complex nature of the oligomeric porphyrins, structural elucidation of all

components and impurities may be difficult; however, the applicant should demonstrate acceptable attempts to properly control and characterize the drug product. For example, in response to Question 11(b), the applicant had withdrawn the UV/VIS method to detect the presence of photo-oxidative degradants, which was previously developed at the Agency's request. Although photophyrins are receptive to photo-oxidation, the drug product will be released without any quantitative data to assure that the drug product is not adversely affected by photo-oxidation during its manufacture and storage, until such time that the CE assay is adequately validated. It is recommended that the Draft CMC Comment be included in the approval letter to remind the applicant that failure to identify and characterize all the components does not absolve the applicant of the responsibility to properly control and qualify the drug product.

The labeling and package inserts were reviewed and comments faxed to the applicant December 8, 1995.

Ying-Ao Hsieh 12-13-95
Ying-Ao Hsieh, Ph.D.
Review Chemist, HFD-150

Rebecca Wood 12-15-95
Rebecca F. Wood, Ph.D.
Supervisory Chemist, HFD-150

cc:
NDA 20-451
HFD-150 Div. File
HFD-150/RHWood
HFD-150/YAHsieh
HFD-150/PZimmerman
R/D Init. By:

Division of Oncology Drug Products
HFD-150
Review of Chemistry, Manufacturing and Controls

NDA #: 20-451 **Chemistry Review #:** 02 **Review Date:** 06-Jun-1995

Submission Type	Document Date	CDER Date	Assigned Date
Amendment (AC)	02-Mar-1995	07-Mar-1995	26-Apr-1995
Amendment (BZ)	12-May-1995	16-May-1995	18-May-1995

Name & Address of Applicant

QLT Phototherapeutics, Inc.
c/o Bogle and Gates
Two Union Square
601 Union Street
Seattle, WA 98101-2346

Drug Product Name:

Proprietary:	Photofrin for Injection
Nonproprietary/USAN:	Porfimer Sodium for Injection
Code Name/Number:	CL 184,116
Chem. Type/Ther. Class:	1P

ANDA Suitability Petition/DESI/Patent Status: N/A

Pharmalogical Category/Indication: Reduction of obstruction and palliation of dysphagia in patients with completely or partially obstructing esophageal cancer

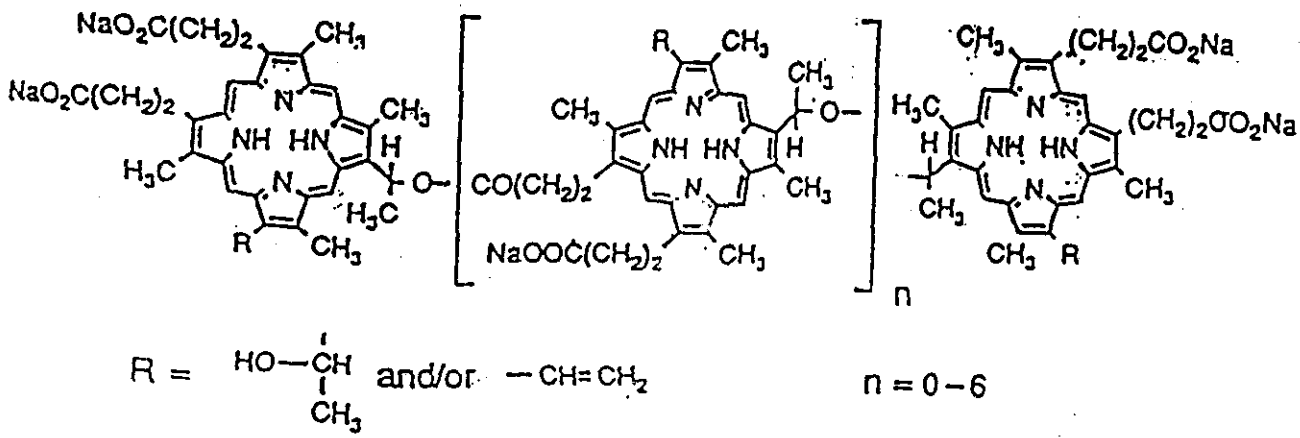
Dosage Form: Lyophilized Sterile Powder for Injection

Strength: 75 mg/vial

Route of Administration: Intravenous Infusion

Dispensed: _x_ Rx ___ OTC

Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:



R = HO—CH(CH3)— and/or —CH=CH2 n = 0 – 6

Supporting Documents: IND 25,064

Related Documents (if applicable):

DMF	DMF
MAF	DMF
DMF	DMF
DMF	DMF

Consults:

Consult	Status	Comments
EER for	pending	Submitted 17-May-1995
DMF	pending	Submitted 17-May-1995
EER for	inspected 23-Jan-95	Form 483 issued
EER for	pending	Submitted 17-May-1995
EER for	pending	Submitted 12-Jan-1995

EER for Lederle Parenterals (DS and DP)	pending	Submitted 12-Jan-1995
Statistics (stability study protocol)	pending	Submitted 18-May-1995
Environmental Assessment	pending	Submitted 10-May-1994

Comments:

I. 2-Mar-1995 amendment (AC)

This amendment provided reposes to the Agency's CC deficiency letter dated 18-Nov-1994, based on existing data, to some of the deficiencies; however, most of the critical issues remain unresolved. They may be categorized as follows:

Composition and Components:
The drug substance was synthesized by

Analytical Method:
The oligomeric mixture was characterized by mass spectroscopy and HPLC. The applicant was not able to determine the mean molecular weight of the polymers by mass spectroscopy. The HPLC conditions provided by the applicant did not resolve the oligomeric conglomerate. The HPLC assay value of the drug product can be considered little more than an estimate of the total oligomer content. The current level of product characterization and control is not adequate to assure the lot-to-lot reproducibility. An analytical method, that is capable of, at a minimum, finger printing the oligomeric mixture should be developed to properly characterize the drug product and to establish its stability under different storage conditions.

II. 12-May-1995 amendment (BZ)

This amendment described a new bioactivity indicating HPLC method for Photofrin in order to eventually replace the mouse bioassay which is used routinely for release and stability testing.

Because the applicant has not been able to identify the active component(s) in the drug product, the Photofrin bioassay was included as a part of the release testing of the drug product to assure its bioactivity. In an attempt to link the bioactivity of Photofrin to its physical attributes, the applicant deeveloped a new bioactivity-indicating HPLC assay.

The applicant has presented enough evedence to demonstrate that there is a qualitative correlation between Photofrin's bioactivity and certain peak area percent values from its HPLC profile, but failed to show that this correlation is a quantitative one. It is recommended that the deficiencies identified should be conveyed to the applicant.

Conclusions and Recommendations:

The deficiencies which are listed in the Draft Deficiency Letter to the Applicant, Chemist's Part, should be communicated to the applicant. It is recommended that all the deficiencies should be fully addressed prior to approval.

Yung-Ao Hsieh 7-5-95

Yung-Ao Hsieh, Ph.D.
Review Chemist, HFD-150

Rebecca H. Wood 7-5-95

Rebecca H. Wood, Ph.D.
Supervisory Chemist, HFD-150

cc:

NDA 20-451
HFD-150/Div. File
HFD-150/CHoiberg
HFD-150/RHWood
HFD-150/YAHsieh
HFD-150/PZimmerman

P Zimmerman

OCT 25 1994

DIVISION OF DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS
HFD-150

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-451 **CHEM.REVIEW #:** 01 **REVIEW DATE:** 17-AUG-94

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	13-APR-94	13-APR-94	18-APR-94
AMENDMENT	17-MAY-94	19-MAY-94	19-MAY-94

REVIEWER: Richard Lowenthal, M.S.

NAME & ADDRESS OF APPLICANT:
QLT Phototherapeutics, Inc.
c/o Bogle and Gates
Two Union Square
601 Union Street
Seattle, WA 98101-2346

DRUG PRODUCT NAME

Proprietary:	Photofrin for Injection
Nonproprietary/USAN:	Porfimer sodium for Injection
Code Name/#:	CL 184,116
Chem.Type/Ther.Class:	1 P

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: Reduction of obstruction and palliation of dysphagia in patients with completely or partially obstructing esophageal cancer.

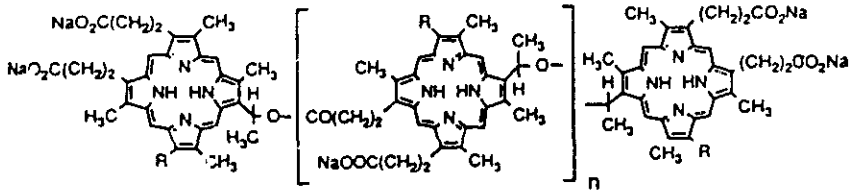
DOSAGE FORM: Lyophilized Sterile Powder for Injection

STRENGTHS: 75 mg/vial

ROUTE OF ADMINISTRATION: Intravenous Infusion

DISPENSED: X Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.Wt.:



R = HO—CH(CH3)— and/or —CH=CH2 n = 0-6

SUPPORTING DOCUMENTS:

IND 25,064

RELATED DOCUMENTS (if applicable):

DMF	DMF
MAF	DMF
DMF	DMF
DMF	DMF

CONSULTS:

Consult	Status	Comments
EER	Pending	Submitted June 13, 1994.
Methods Validation	Hold	Will be initiated once all methods deficiencies have been addressed.
Microbiology	Pending	Sent on May 13, 1994
Statistics	Hold	Stability data and protocol deficiencies must be addressed.
Environmental Ass.	Pending	Sent on May 10, 1994

REMARKS/COMMENTS: The drug substance is manufactured by three different firms.

manufactures the Hp diacetate and ships this to facility for oligomerization and aseptic filling of the drug product. The drug substance is a hematoporphyrin polymer and consists of a mixture of oligomers with chain lengths of n=2 to 8. The hematoporphyrin units can also be linked by either an ether or ester bond. As a result of these features and due to the fact that a mixture of is used in the production, there exists The drug substance and product attributes have been poorly studied and the test methods proposed for regulatory control do not adequately take into account significant properties of the drug. Due to the inability to accurately analyze the drug substance, much of the data provided is of limited use. Additional analytical methods capable of evaluating the oligomer ratios, ether/ester ratios, amount of olefinic impurity and the amount of other substance will be needed. A number of routine methods are also not adequately employed (e.g. particulate matter testing). The sponsor has been previously warned during the IND process, that these issues would be significant once an NDA is submitted. The applicant has made only a minimal effort in adequately characterizing and controlling the compound.

CONCLUSIONS & RECOMMENDATIONS:

NDA 20-451 is **NOT APPROVABLE** from a chemistry manufacturing and controls perspective and a deficiency letter should be conveyed to the sponsor. The deficiencies will need to be addressed before the NDA can be approved.

Richard E. Lowenthal

Richard Lowenthal, M.S.
Review Chemist, HFD-150

cc:
Orig. NDA 20-451
HFD-150/Division File
HFD-150/RLowenthal
HFD-150/CSO/PZimmerman – 2 copies
HFD-150/JBlumenstein
HFD-102/CKumkumian [#1 only]
R/D Init by: SUPERVISOR
filename: N20451rl.000

11/25/94

P. Zimmerman

DEC 12 1995

REVIEW for DIVISION OF ONCOLOGIC DRUG PRODUCTS , HFD-150
OFFICE OF NEW DRUG CHEMISTRY, MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW NO. 3
December 12, 1995

Reviewing Microbiologist: Carol K. Vincent, HFD-805

A. 1. NDA NUMBER: 20-451 / AZ

PRODUCT NAME: Photofrin (Porfimer Sodium)

APPLICANT: QTL Phototherapeutics, Inc *
c/o Bogle and Gates
Two Union Square
601 Union Street
Seattle, WA 98101-2346

* a US subsidiary for: Quadra Logic Technologies, Inc. (QTL)
520 W. 6th Avenue
Vancouver, British Columbia, Canada V5Z 4H5

MANUFACTURER: Lederle Parenterals, Inc.
Carolina, Puerto Rico 00987

2. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Lyophilized powder in 40 cc glass vial with 20mm rubber stopper and aluminum seal; for intravenous use after reconstitution.

3. METHOD(s) OF STERILIZATION: Aseptic fill

4. PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION: Porphyrin photosensitizer for photodynamic therapy for treatment of primary or recurrent obstructing esophageal carcinoma.

5. DRUG PRIORITY CLASSIFICATION: 1 P

B. 1. AMENDMENT DATE: 12-04-1995
2. RECEIVED FOR REVIEW: 12-07-95
3. AMENDMENT ASSIGNED: 12-07-95
4. USER FEE DUE DATE: 12-06-96
5. REGULATORY DUE DATE: 06-06-96

C. REMARKS: This amendment responds to the Division of Oncologic Drug Products' Approvable Letter dated July 13, 1995. This same letter conveyed the Microbiology deficiencies to the applicant [see MICROBIOLOGIST'S REVIEW NO. 1 DATED MAY 15, 1995 in which we recommended approval if the applicant committed to provide the additional information for the microbiology deficiencies on a post-approval basis]. The applicant chose to provide responses for parts of the requested information at this time [subject of this review], and also chose to provide the filter sterilization validation information after its completion by the contractor, estimated by the applicant to be July 1996.

D. RECOMMENDATION:

We recommend approval for NDA 20-451, Photofrin, based on the microbiological quality and sterility assurance information submitted in the application and amendments. The applicant has committed to respond to the final microbiological quality and sterility assurance issue concerning filter sterilization process validation information provided to the applicant by the contractor. The applicant expects to provide this additional information in July, 1996.

See "E. REVIEW NOTES:", below.

Carol K. Vincent 12-12-95

Carol K. Vincent, HFD-160

FTK 12/12/95

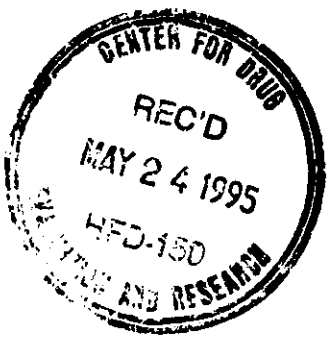
cc:
Orig. NDA 20-451/AZ
HFD-150/Zimmerman
HFD-160/Consult File/CKVincent [HFD-805]
Draft: CKVincent/12-08-95/12-12-95
R/D Init: PCooney/12-12-95
HFD-150/RWood
" /YHuich

6/2/95 ↔ Zimmerman

MAY 15 1995

CONSULTATIVE REVIEW TO HFD-150
DIVISION OF MEDICAL IMAGING, SURGICAL, AND DENTAL DRUG PRODUCTS
MICROBIOLOGIST'S REVIEW NO. 1
May 15, 1995

Reviewing Microbiologist: Carol K. Vincent



A. 1. NDA NUMBER: 20-451

PRODUCT NAME: Photofrin (Porfimer Sodium)

APPLICANT: QTL Phototherapeutics, Inc *
c/o Bogle and Gates
Two Union Square
601 Union Street
Seattle, WA 98101-2346

* a US subsidiary for: Quadra Logic Technologies, Inc. (QTL)
520 W. 6th Avenue
Vancouver, British Columbia, Canada

MANUFACTURER: Lederle Parenterals, Inc.
Carolina, Puerto Rico 00987

clinical studies conducted under IND were sponsored by:

Lederle Laboratories,
a Division of American Cyanamid
401 N. Middletown Road
Pearl River, New York 10965-1299

2. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Lyophilized powder in 40 cc glass vial with 20mm rubber stopper and aluminum seal; for intravenous use after reconsitiution.

3. METHOD(s) OF STERILIZATION: Aseptic fill

4. PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION: Porphyrin photosensitizer for photodynamic therapy for treatment of primary or recurrent obstructing esophageal carcinoma.

5. DRUG PRIORITY CLASSIFICATION: 1 P

B. 1. DOCUMENT DATE: 04-12-94

2. AMENDMENT: 05-13-94

3. ASSIGNED: 06-06-94

2. RELATED DOCUMENTS:

IND Lederle Laboratories)

DMF

DMF

]

DMF

C. REMARKS: The NDA submitted by QTL Phototherapeutics, Inc. is Part I of a multipart application for a combination drug and device product consisting of the photoactive drug, Photofrin (porfimer sodium) submitted to the Center for Drug Evaluation and Research (CDER), and three device Premarket Approval Applications submitted to The Center for Devices and Radiological Health (CDRH). Clinical studies for this NDA were conducted under IND The Division of Oncology and Pulmonary Drug Products (HFD-150) is the reviewing division; CDER is the lead and responsible center for this combination product. The drug Photofrin was designated a treatment for life-threatening and severely debilitating disease (per 21 CFR 312 Subpart E) on April 22, 1991, and granted orphan drug designation on June 6, 1989.

Only the microbiological and sterility assurance aspects of the aseptic fill manufacturing process for Photofrin (porfimer sodium) manufacture are covered in this review. The applicant provided an amendment dated May 13, 1994 responding to the HFD-150 Chemistry reviewer's request for information concerning validation of the sterile manufacturing process (subject of this review).

D. RECOMMENDATION: We can recommend approval for sterility assurance for NDA 20-451 provided the applicant commits to provide on a post-approval basis the additional sterilization process validation information requested in the DRAFT OF LETTER TO APPLICANT, below. Photofrin is a high priority drug submitted under the Prescription Drug User Fee Act, is an orphan drug, and a designated treatment under 21 CFR 312 Subpart E (see Remarks, above). Although there are specific deficiencies in the application's documentation, we do not feel the lyophilized drug product, as currently described, constitutes an imminent public health hazard because of the chemical nature of the drug substance and the harsh physiochemical conditions (heat, acid, base, pH extremes) of its processing and manufacture. The specific requests for additional or clarifying information should be conveyed to the applicant.

Carol K. Vincent 5-15-95

Carol K. Vincent, HFD-160

Date 5/15/95

cc:
Orig. NDA 20-451
HFD-150/Zimmerman/JSchwab/GWilliams/YHsieh
HFD-160/Consult File/CKVincent
Draft: CKVincent/10-25-94/03-24-95/05-08-95
R/D Init: PCooney/05-12-95

Division of Oncology and Pulmonary Drug Products
Review and Evaluation of Pharmacology and Toxicology Data
NDA Consult #1 and #2

NDA 20-451 Reviewer: W. David McGuinn, Jr.,Ph. D.

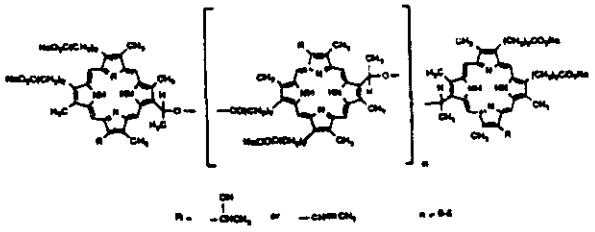
Submission:	NDA	April 12, 1994
	Consult #1	May 31, 1994
	Consult #2	May 12, 1995
	Completed	June 27, 1995

Sponsor: QLT Phototherapeutics Inc.,
520 West 6th Avenue
Vancouver. British Columbia
Canada, V5Z 4H5

Information to be conveyed to the sponsor: ~~YES~~ NO

Drug Name: Photofrin® (Porfimer Sodium), or Photofrin II
Chemical Name: Dihematoporphyrin Esters

Structure



Indications: Esophageal Cancer

Partial list of Related IND's and NDA's

IND

IND

The FDA granted Photofrin orphan drug designation June 6,1989 for use against esophageal carcinoma. On April 22. 1991, the FDA granted Photofrin designation as a drug intended to treat life-threatening and severely debiiitation diseases under 21 CFR 321 Sub-part E for esophageal cancer.

Dosage Forms and Route of Administration:

Photofrin® is administered *i.v.* in dextrose$_{(aq)}$ (5%) or 0.9% Sodium Chloride (USP) at a dose of 2.0 mg/kg (74 mg/m^2). It is reconstituted from a lyophilized powder. Forty to 50 hr after dosing, 630 nm light from a laser is transmitted to the tumor site through an optical fiber light guide at a predetermined power and energy.

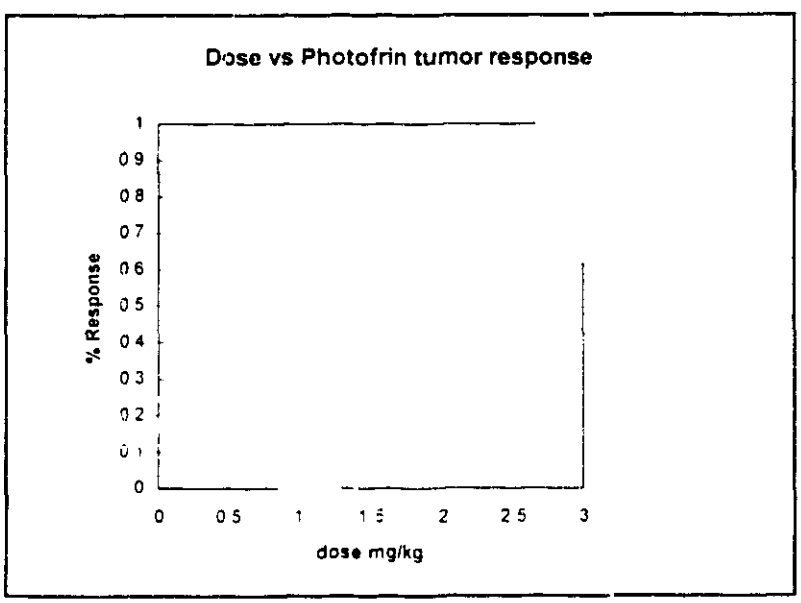
Review of the Standard Operating Procedure for The Biological Assay of PHOTOFRIN

Initially, QLT had no chemical method of assuring PHOTOFRIN potency. They can not isolate the active components within the mixture. To assure that each batch of PHOTOFRIN was therapeutically equivalent, the sponsors developed a biological assay (protocol TX-3001(1) volume 5B original NDA submission p 154).

In this assay 15 DBA/2 mice were implanted with SMT-F tumor subcutaneously. When the tumor was palpable the mice were injected with 4.2 mg/kg PHOTOFRIN i.p. Note that this dose is only 17% of the clinical dose on a mg/m^2 basis. Eighteen to 26 hours after dosing a minimum of ten mice with measurable tumor between four and six mm in diameter were selected. The investigators restrained the mice and irradiate the area of skin above the tumor with white light from a xenon arc lamp. The energy density was mW/cm^2 with a beam diameter of cm. The irradiation time was minutes.

The investigators monitored the mice for seven days, then examined them for tumors. Those mice with no palpable tumor were considered responders. Those with any detectable tumor were considered non-responders. If more than 50% of the mice responded, the batch passed. If less than 50% of the mice responded, the another group 20 mice was tested. QLT passed a batch as good if after this retest greater than 50% or 15 of 30 responded.

The FDA pointed out that this test could not detect a superpotent batch of PHOTOFRIN and requested changes in the assay. QLT then developed a two sided assay (protocol TX-30[illegible]), volume 5B, original NDA submission, p 176) that could characterize both subpotent and superpotent batches of PHOTOFRIN. In this assay at least 13 mice are tested. This increase was needed to achieve the power necessary in a two sided test. The interval between dosing and irradiation was increased to a maximum of 28 hours to make the test more practical for the investigators. The sponsor specified that after 20 test assays, investigators will do an assay with a designated standard batch of PHOTOFRIN to assure consistency in the procedure. Lastly, QLT lowered the standard dose to 1.8 mg/kg. This dose is the ED_{50} determined from twelve assays from four different batches. The following graph shows the dose response curve for this new assay.



The more rigorous procedure also seems to have lowered the amount of PHOTOFRIN required for 50% response. but the sponsor did not identify the factors contributing to this increased effectiveness. In this new assay, QLT considers a batch to be acceptable if $3 \leq$ tumor response ≤ 9. The protocol provides for a retest with 13 more mice if the initial test fails and considers the batch to pass if the combined result after retest is $7 \leq$ tumor response ≤ 17.

Using this dose response curve, QLT estimated the expected cure rates for PHOTOFRIN batches of different potency relative to the standards used to generate the curve. The following table shows the probability that a batch with a specified potency relative to standards will pass this assay.

Potency relative to standards	Expected cure rate	Probability of passing	Probability after 2nd assay
50%	0.05	**0.02**	0.00
70%	0.20	**0.50**	0.06
100%	0.50	**0.94**	0.69
130%	0.73	**0.48**	0.07
150%	0.83	**0.17**	0.00

The sponsor assumed a binomial distribution for the responses. I confirmed these calculations using the binomial function of Microsoft Excel. The table shows that the assay is skewed to allow higher probability of accepting a superpotent dose than a subpotent dose with the same deviation from the standard. The probability of accepting a bad batch greatly diminishes after the second assay but the cost of the assay goes up rapidly with the number of mice used. The sponsor is appropriately concerned about minimizing the use of mice. Nevertheless, the probability of accepting a batch that is 1.5 times as potent as the reference standards is nearly 1 in 5. A standard dose of such a batch would be equivalent to a dose of 3 mg/kg of PHOTOFRIN. This dose is above the maximum tolerated dose. If the sponsor made the upper cut off for the assay 8 mice responding, the probability of accepting a dose 150% as potent drops to 0.055. If a maximum of seven mice are allowed to respond in the assay the probability of accepting a dose 150% as potent as standards drops to 0.014. Nevertheless, these probabilities are based on crude estimates. The variability of the assay is possibly greater than the variability of the synthetic process. The following table shows the variability of the assay among batches. A response of 9 among 13 would be nearly three standard deviations from the mean for this group.

Dose mg/kg	Batch	response mice/total	% response	
1.80	P91-0163	5/10	0.500	
1.80	P91-0163	4/10	0.400	
1.80	150A028P	6/13	0.462	
1.80	200A026P	7/13	0.538	
1.80	201A027P	7/13	0.538	
1.80	15105B-101A	2/6	0.333	
			0.462	mean
			0.082	std dev
			0.18	std dev ~ mean

In the NDA submission the sponsor also validated equivalence of results from two laboratories QLT and Oncologic Foundation of Buffalo (OFB) (vol. 5B, p 136). This validation is undated and from the text, I must assume that the sponsor used the initial assay (TX-3001(1)). Nevertheless, the report shows an appreciation for the difficulties associated with the assay and demonstrates that two different laboratories can achieve reasonably consistent results. QLT also submitted a study that showed that the results of the assay were not significantly affected when the DBA/2 mice were seropositive for mouse hepatitis virus. Finally, QLT submitted a study characterizing the variation of response that resulted when they used different xenon arc lamps (Vol. 5B).

This is a very difficult, expensive and time consuming assay. This technique for determining batch to batch consistency for drug potency is unusually sensitive to investigator technique. The results could easily drift over time. Nevertheless, within its many limits the assay does adequately define batch potency as a function of response. The assay can distinguish between subpotent, potent and superpotent batches with some statistical confidence.

Recommendation

This assay is adequate to determine batch-to-batch potency of PHOTOFRIN so long as the sponsors can continue to compare results back to those obtained from the standard samples every 20 assays.

W. David McGuinn, Jr., Ph. D.

June 28, 1995

cc:
Original NDA
HFD-150
HFD-150/W D McGuinn
HFD-150/J J DeGeorge
HFD-150/P Zimmerman
HFD-150/G Williams
HFD-150/Y Hsieh

6/28/95

June 28 95

E. A.

+

Fons;

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Photofrin®

(porfimer sodium)

Injection

NDA 20-451

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ONCOLOGY and PULMONARY DRUG PRODUCTS (HFD-150)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-451

Photofrin®

(porfimer sodium)

Injection

The Food and Drug Administration (FDA) recognizes the National Environmental Policy Act of 1969 (NEPA) as the national charter for protection, restoration, and enhancement of the environment. NEPA establishes policy, sets goals (section 101), and provides procedures (section 102) for carrying out the policy.

Environmental information is to be available to the public and the decisionmaker before decisions are made about actions that may significantly affect the quality of the human environment; FDA actions are to be supported by accurate scientific analyses; and environmental documents are to concentrate on timely and significant issues, not to amass needless detail.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **Photofrin®**, **QLT PhotoTherapeutics, Inc.** has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Porfimer sodium is a synthetic drug which is administered as an injectable solution in the treatment of primary or recurrent obstructing esophageal carcinoma. The drug substance will be manufactured at Lederle Laboratories, Pearl River, NY and Lederle Parenteral Inc. Carolina, Puerto Rico. The drug product will be manufactured at Lederle Parenteral Inc. Carolina, Puerto Rico. The finished drug product will be used in hospitals and clinics.

Porfimer sodium may enter the environment from patient excretions or small amounts from manufacturing operations. Chemical and physical test results indicate that the compound will most likely be restricted to the aquatic environment.

As porfimer sodium is expected to persist in the aquatic environment for some time, the toxicity to organisms was characterized. Acute static toxicity studies in water fleas (*Daphnia magna*) indicate that the drug substance is not toxic at the expected environmental concentrations nor is there inhibition of microorganism

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned and expired drug product and production waste is disposed of at a licensed landfill while rejected drug product will be disposed of at a licensed incineration facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

6/26/95 Nancy B Sager
DATE Prepared By
Nancy B. Sager
Environmental Scientist
Center for Drug Evaluation and Research

6/27/95 Robert A. Jerussi
DATE Concurred
Robert A. Jerussi, Ph.D.
Associate Director for Chemistry
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Compliance Statements
Material Safety Data Sheet

CC: Original NDA 20-451/PZimmerman copy to NDA/HFD-150
FONSI File 20-451/HFD-004
Docket File/HFD-004
FOI Copy/HFD-019

20451.FON
F/T by NBS 06/26/1995

PHOTOFRIN® sterile porfimer sodium

CL 184,116

Environmental Assessment

JUNE 1995

Lederle Laboratories
Pearl River, New York 10965

TABLE OF CONTENTS

1. DATE

June, 1995

2. NAME OF APPLICANT

QLT PhotoTherapeutics, Inc.

3. ADDRESS

Two Union Square, 601 Union St., Seattle, Washington 98101-2346.

4. DESCRIPTION OF THE PROPOSED ACTION

4.1 Requested Approval

Porfimer sodium is the active ingredient in PHOTOFRIN® sterile porfimer sodium. Approval is requested for manufacturing and marketing the formulated product, which is supplied as a lyophilized powder for intravenous injection at a dosage strength of 75 mg/vial. This assessment statement addresses the introduction of porfimer sodium into the environment and related environmental considerations.

4.2 Need

PHOTOFRIN® porfimer sodium is effective in photodynamic therapy in patients with primary or recurrent obstructing (either partially or completely) esophageal carcinoma. For advanced disease, treatment with PHOTOFRIN® has effected palliation of the malignant dysphagia resulting in an improved quality of life. PHOTOFRIN® has been granted orphan drug status for esophageal cancer.

4.3 Manufacturing Locations

The hematoporphyrin diacetate intermediate will be made at Lederle Laboratories, Middletown Road, Pearl River, N.Y. The finished bulk and drug product will be manufactured at Lederle Parenterals, Inc., 65th Infantry Avenue, Km 9.7, Carolina, Puerto Rico.

4.3.1 Hematoporphyrin Diacetate Manufacture

Porfimer sodium is prepared in a two-step synthesis from the monomeric heme derivative hematoporphyrin dihydrochloride, and exists as a mixture of oligomers. Step 1 of the synthesis (hematoporphyrin diacetate preparation) will be carried out at Lederle Laboratories in Pearl River N.Y. A letter indicating compliance of the Pearl River site with the air aqueous and solid emission requirements set forth in applicable federal, state and local statutes and regulations (Appendix 1).

Lederle Laboratories is located on Middletown Road, Pearl River, N.Y., on a 528-acre site containing over 160 buildings and bounded by security fencing. The plant site is guarded on a 24-hour basis by trained security personnel. The facility is located in a populous area with a temperate climate and flat terrain.

4.3.2 Dosage Form Manufacture

Conversion of the diacetate to porfimer sodium, diafiltration, and lyophilization and packaging of the PHOTOFRIN® 75 mg/vial dose strength will be carried out at the Lederle Parenterals Inc. site in Carolina, Puerto Rico. The parenteral product process is in compliance with all local requirements, as noted in the attached environmental compliance certification statements from Lederle Parenterals, Inc., Carolina, Puerto Rico, and compliance certification from the local authorities (Appendix 2).

Lederle Parenterals and Piperacillin, Inc. is located at 65 Infantry Avenue, KM 9.7, Carolina, Puerto Rico 00630. It is a 19-acre site containing seven major buildings and bounded by security fencing. The facilities are located in a populous area with a subtropical climate and flat terrain. Production is limited to parenteral solutions, suspensions and freeze-dried powders.

4.4 Location of Use and Disposal

Sterile porfimer sodium will be used in major medical centers throughout the United States and in international markets. According to established procedures conforming to federal, state and local regulations, the returned and expired goods are shipped to a permitted disposal facility and landfilled. Rejected PHOTOFRIN® batches are shipped to a permitted facility for high-temperature incineration.

4.5 Conclusion

PHOTOFRIN® is synthesized at the Lederle Laboratories, Pearl River, N.Y. and Carolina, P.R. plants. Both sites are in compliance with applicable environmental regulations. Procedures are in place for disposal of returned, expired and rejected drug product at permitted facilities.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES

The physical and chemical properties of porfimer sodium are summarized in this section. The material safety data sheet (MSDS) for porfimer sodium is included in the documentation (Appendix 3).

5.1 Description of Active Substance

5.1.1 USAN Name

Porfimer sodium

5.1.2 Nomenclature (CAS)

Not Applicable.

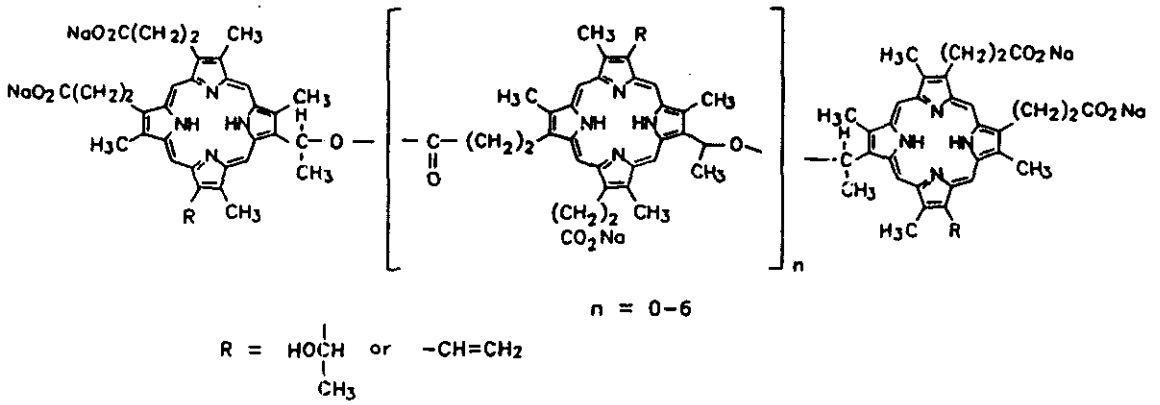
5.1.3 Laboratory Code Number

CL 184,116

5.1.4 CAS Number

Not Applicable

5.1.5 Structure



n = 0–6

R = $HOCH(CH_3)$ or $-CH=CH_2$

5.1.6 Molecular Formula

Not Applicable

5.1.7 Molecular Weight

Not applicable; porfimer sodium is a mixture of oligomers. Depending upon the number of hematoporphyrin units and dehydration, the MW would be in the area of 1178 to about 4659.

5.2 Physical/Chemical Characteristics

Porfimer sodium lyophilized powder is a dark red solid soluble in water and methanol, and insoluble in methylene chloride. Fast Atom Bombardment (FAB) mass spectral data indicate that the weighted average oligomer length ranges from 2-3 porphyrin units/oligomer. The units are connected by both ether and ester linkages. Vapor pressure, n-octanol/water partition, water solubility and hydrolysis studies are described in Section 7.

5.3 Impurities and Degradation Products

5.3.1 Bulk Drug

The impurities consist principally of three known related compounds (monomeric porphyrins). Specifications have been established to control the level of the impurities and to assure batch to batch consistency of the drug substance.

5.3.2 Dosage Form

Purity profiles for representative batches demonstrate acceptable levels of related compounds.

5.4 Additives

The components of PHOTOFRIN® sterile porfimer sodium, 75 mg vial, are shown below.

Component	Rationale
Porfimer Sodium	Active Ingredient
Nitrogen, NF	Vial Headspace
Sodium Hydroxide NF	pH Adjustment if needed
Hydrochloric Acid NF	pH Adjustment if needed

5.5 Conclusion

Specifications for both drug substance and product have been established. The additives used for formulation are NF grade materials. The material safety data sheet for porfimer sodium is included in the documentation.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

This section deals with the introduction of porfimer sodium into the environment due to the production and disposal as well as the therapeutic use of PHOTOFRIN®.

6.1 Introduction of Substances into the Environment Due to Production and Disposal

6.1.1 Synthesis of Hematoporphyrin Diacetate

Hematoporphyrin dihydrochloride is converted to hematoporphyrin diacetate under cGMP conditions at Lederle Laboratories, Pearl River, N.Y. The facilities, emission controls and waste disposal at the site are in compliance with all applicable air aqueous and solid waste environmental regulations as noted in the attached environmental compliance certification statement from Lederle Laboratories (Appendix 1).

6.1.1.1 Workplace

Chemicals in the workplace are stored, handled and managed in accordance with cGMP standards. Ventilation and air filtration are employed to assure containment of chemicals and minimal exposure of workers and the workplace to chemicals. Current GMP regulations are followed for all equipment and operating procedures. Personal protection is provided by the use of gear such as respirators and gloves.

6.1.1.2 Atmosphere

Dusts and volatile materials are generated during the synthetic process. The exhaust stack is equipped with HEPA filters (99.7% efficiency). As noted above, Lederle Laboratories has secured the applicable air permits.

6.1.1.3 Aqueous Waste Streams

The aqueous process waste stream including waste from the cleaning of equipment is released into the plant effluent which is composed of ground water, storm water and process effluents. This waste stream is delivered to the on-site pretreatment plant which provides biological (UNOX®) treatment to the site waste water stream. The plant effluent is in compliance with all applicable environmental regulations and permits and is conducted to the Orangetown publicly owned treatment works (POTW) which provides further biological treatment prior to discharge to the Hudson River.

6.1.1.4 Solid Waste

Rejected goods and solid waste consisting of protective personnel gear, spent cartridge filters, filter cloths and papers, polyethylene tray liners, tyvec tray covers and sweepings from the manufacturing processes are collected and shipped to a permitted facility and subsequently landfilled.

6.1.2 Dosage Form Production

The second step of the porfimer sodium synthesis, and preparation of the final product is carried out at the Carolina, Puerto Rico plant. The parenteral product formulation process is in compliance with all local requirements, as noted in the attached environmental compliance certification statement from Lederle Parenterals, Inc., Carolina, PR, and compliance certification from the local authorities.

6.1.2.1 Workplace

Chemicals in the workplace are stored, handled and managed in accordance with cGMP standards. Engineering and work practice controls are employed to assure containment of chemicals and minimal exposure of workers and the workplace to chemicals. Current GMP regulations are followed for all equipment and operating procedures.

6.1.2.2 Atmosphere

HEPA filtration controls the emission of particulates from the glove box exhaust system and the aseptic production area. The emission controls employed in the production area are in compliance with applicable local regulations, as established by the PR Environmental Quality Board.

6.1.2.3 Aqueous Waste Streams

Aqueous process washings are delivered to the on-site pretreatment plant prior to release to the municipal water treatment facility. The effluent is equalized, agitated and aerated to reduce its chemical and biological oxygen demand to comply with the sewer discharge regulation as established by the Puerto Rico Aqueduct and Sewers Authority (PRASA). The plant effluent is conducted to the municipal water treatment facility which provides further dilution.

6.1.2.4 Solid Waste

Rejected goods and solid waste consisting of protective personnel gear, spent cartridge filters, dust from dust collectors and sweepings from the manufacturing processes are collected and shipped to a permitted facility for high-temperature incineration.

6.1.3 Disposal

Returned PHOTOFRIN® vials will be ultimately landfilled at a permitted disposal site.

6.2 Introduction Into the Environment Due to Therapeutic Use

Metabolism studies in laboratory animals indicate that the major route of excretion is fecal. It is assumed that the amount excreted is equivalent to the amount dosed.

6.3 Conclusion

PHOTOFRIN® bulk drug and the 75 mg/vial dosage form are manufactured at facilities that are in compliance with all applicable environmental requirements. Review of production procedures indicates that environmental emissions will not exceed the applicable environmental permit levels. All rejected drug product is transported to a permitted disposal site for high temperature incineration. Returned goods are landfilled.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

7.1 Physical Characteristics

The physical properties of porfimer sodium indicate that it will be present in the aquatic compartment of the environment. The vapor pressure is estimated to be $<2 \times 10^{-11}$ torr at 25°C. Aqueous solubility is <0.002 mg/mL, 252 mg/mL and >402 mg/mL at 20°C for pH's of 5, 7 and 9, respectively. The partition coefficients (P_{ow}) for porfimer sodium in an octanol/water system have been determined at pH 7 and 9. The log P_{ow} values (24°C) were -1.5 (pH 7) and -2.3 (pH 9). The partition coefficient was not determined at pH 5 because pretest data indicated no detectable test substance solubility in aqueous pH 5 buffer. These data collectively place porfimer sodium into the aqueous phase of the environment as defined by the PMA Environmental Assessment Guidelines.[1]

7.2 Metabolism

The metabolism of PHOTOFRIN® in humans or in animals has not been fully defined. Data in laboratory animals indicate that the major route of excretion is fecal (40-60% in 7-8 days). Since no human metabolism data are available it is assumed that the doses administered will ultimately be introduced into the environment as PHOTOFRIN® itself, as monomeric degradation products or as further degradation products resembling those of the natural product heme.

7.3 Hydrolysis

These studies were conducted according to FDA Technical Assistance Handbook Document #3.09. Tests at pH 5 were not performed, because the pretest water solubility data showed no detectable solubility in aqueous pH 5 buffer. Preliminary 5-day hydrolysis tests at 50°C were performed at pH 7 and 9. As directed in the FDA Technical Assistance Handbook, follow-up tests were not conducted, due to limited hydrolysis in the preliminary test at 50°C (less than 10% in 5 days). The

[1] Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA (PMA, 1991).

data indicate that hydrolysis provides minimal degradation of porfimer sodium in the environment.

7.4 Conclusion

Use of PHOTOFRIN® will result in emission of porfimer sodium into waste water streams. The physical properties of porfimer sodium indicate that it will enter the aquatic compartment of the environment.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

8.1 Evaluation of Toxicological Effects

The effects of porfimer sodium have been evaluated using (1) inhibition of growth of pure cultures of bacteria, fungi, and blue-green algae, and (2) toxicity to a representative planktonic macroinvertebrate (Daphnia magna) as markers for potential environmental toxicity.

The *Microbial Inhibition with porfimer sodium* study was conducted in compliance with FDA Environmental Assessment Technical Assistance Handbook Document (TAD) No. 4.02. No inhibition of growth was observed for any of the test organisms at any concentration studied, up to and including 1000 mg/L porfimer sodium (ppm).

In the second study, *Acute Toxicity of porfimer sodium to Daphnia magna,* conducted in compliance with FDA TAD No. 4.08, the 24- and 48 hr EC_{50} values for porfimer sodium were both >994 mg/L.

A wide safety margin is indicated for porfimer sodium in the environment. The degree of safety is several orders of magnitude in excess of the 100-fold safety factor recommended in the PMA Environmental Assessment Guidelines.[2]

Based upon these data, no environmental hazard would be expected due to the manufacture, disposal and use of porfimer sodium.

8.2 Conclusion

Comparison of the MEEC for porfimer sodium with the 48-hr Daphnia EC_{50} indicates a wide margin of safety for porfimer sodium in the environment at the projected level of production. No environmental hazard would be expected due to the manufacture, disposal and use of PHOTOFRIN® porfimer sodium.

---

[2] Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA (PMA, 1991).

9. USES OF RESOURCES AND ENERGY

It is not anticipated that the proposed action will have a significant environmental impact since PHOTOFRIN® is proposed for limited use, and is a semi-synthetic product which possesses the porphyrin ring structure.

9.1 Land Use

No new manufacturing facilities will be constructed at the Carolina, P.R. or Pearl River, NY sites, nor will additional land be acquired in order to produce PHOTOFRIN® at the forecasted levels.

9.2 Mineral Use

No direct use of minerals occurs in the production of PHOTOFRIN®.

9.3 Energy Use

9.3.1 Manufacturing

The production of PHOTOFRIN® at the forecasted levels is associated with a minimal use of energy.

9.3.2 Transportation

No unusual transportation demands due to distribution of PHOTOFRIN® are expected.

9.3.3 Disposal

As indicated in Section 6, rejected or outdated materials will be transmitted to a permitted facility for final disposal.

9.4 National Historical Site and Endangered Species Impact

There are no known effects on historic sites due to the synthesis of porfimer sodium. Since manufacturing at both sites is carried out based upon applicable environmental guidelines, no effect on wildlife, including endangered or threatened species, is anticipated.

9.5 Conclusion

The production of PHOTOFRIN® sterile porfimer sodium will be carried out with a reasonable use of energy and resources. No effect upon national historical sites or endangered species is anticipated.

10. MITIGATION MEASURES

The production of porfimer sodium bulk drug substance and the dosage form will be carried out in accordance with all applicable environmental requirements. Worker safety programs are in place to assure containment of chemicals and minimal exposure of the workers to porfimer sodium.

11. ALTERNATIVES TO THE PROPOSED ACTION

The alternative to the action is discontinued production and marketing of PHOTOFRIN®. We consider this to be unacceptable since an orphan drug which is a valuable therapeutic agent would be removed from the marketplace. It is not anticipated that approval of this proposal will have a negative environmental effect.

12. LIST OF APPENDICES

1. Lederle Laboratories Environmental Compliance Statement for the Pearl River, N.Y. facilities.
2. Lederle Parenterals Environmental Compliance Statement for the Carolina, Puerto Rico Site.
3. Material Safety Data Sheet for PHOTOFRIN® Porfimer Sodium.

13. CERTIFICATION

The undersigned official assures that the information presented is true, accurate and complete to the best knowledge of Lederle Laboratories.

20 June 1995

R. Saunders, Ph.D.
Senior Director
Formulations Research
Lederle Laboratories

Date

APPENDIX 1

Lederle Laboratories Environmental Compliance Statement for the Pearl River, N.Y. facilities

GENERAL COMPLIANCE STATEMENT

Lederle Laboratories, a division of American Cyanamid Company, states that it is in compliance with the air, solid and aqueous emission requirements set forth in permits applicable to the production of Photofrin® at its facilities in Pearl River, New York, as well as air, solid and aqueous emission requirements set forth in applicable Federal, state and local statutes and regulations applicable to the production of Photofrin® at its facilities in Pearl River, New York.

Michael T. Kontaxis

Michael T. Kontaxis, P.E.
Manager, Environmental
Technology Department

June 12, 1995

MTK:sa
m0612951.doc

APPENDIX 2

Lederle Parenterals Environmental Compliance Statement for the Carolina, Puerto Rico Site

LEDERLE PARENTERALS, INC.
LEDERLE PIPERACILLIN, INC.

SAFETY AND ENVIRONMENTAL DEPARTMENT

TO: M. OROURKE

FROM: A. CERVONI AHC

DATE: DECEMBER 3, 1993

ENVIRONMENTAL COMPLIANCE STATUS

ACCORDING TO THE INSPECTION PERFORMED BY THE ENVIRONMENTAL QUALITY BOARD,RCRA DIVISION, ON MAY 19, 1993, THE COMPANY WAS FOUND IN COMPLIANCE WITH THE REQUIREMENTS OF THE REGULATION FOR THE CONTROL OF HAZARDOUS AND NON-HAZARDOUS SOLID WASTES AND FEDERAL REGULATION 40 CFR PART 262. PLEASE, FIND ENCLOSED THE INSPECTION REPORT.

IF YOU NEED ANY OTHER INFORMATION, PLEASE CONTACT ME AT YOUR CONVENIENCE.

FILE (A:ACEQB-3) DISK A

COMMONWEALTH OF PUERTO RICO / OFFICE OF THE GOVERNOR

Environmental Quality Board

July 6, 1993

Ms. Annette Cervoni
Environmental Safety Engineer
Lederle Parenterals and Piperacillin, Inc.
P. O. Box AC Pueblo Station
Carolina, Puerto Rico 00628-4904

Dear Ms Cervoni:

Reference is made to the inspection performed to Lederle Parenterals and Piperacillin, Inc. on May 19, 1993, by Mrs. Nyrka Rosario of the Land Pollution Control Area.

At the time of the inspection, the company was found in compliance with the Regulation for the Control of Hazardous and Non - Hazardous Solid Wastes (RCHNHSW) and 40 CFR 262 and 265.

This compliance letter is related only and exclusively with the above mentioned inspection and does not preclude from further enforcement action.

We appreciate your cooperation.

Cordially,

Roberto Berberena Collazo
Director
Land Pollution Control Area

NR/sec

ESTADO LIBRE ASOCIADO DE PUERTO RICO / OFICINA DEL GOBERNADOR

Junta de Calidad Ambiental

ATTACHMENT VII

*
*
*AREA CONTROL CONTAMINACION DE TERRENOS
*
*

LICENCIA PARA OPERAR FACILIDADES DE DESPERDICIOS SOLIDOS NO PELIGROSOS

Municipio
Carolina

Tipo de Facilidad: Sistema de Incineración de Desperdicios Sólidos No Peligrosos Commercial Incineration Corp. (Celestium)

Dirección: SI-93-0002

Dueño y/o Administrador: Sr. Carlos E. Rodríguez Pardo

Fecha exp.: 18 de enero de 1993 Vence en: 19 de enero de 1997

La Junta podrá revocar o suspender esta licencia si se comprueba que se ha incurrido en alguna violación de las Reglas o Reglamentos vigentes.

Héctor Russe Martínez
Presidente

Fernando Román Pérez
Vice-Presidente

Francisco José Martín-Caso
Miembro Asociado

VJH/fsp

APPENDIX 3

Material Safety Data Sheet for PHOTOFRIN® Porfimer Sodium

DATE: 06/09/95

MATERIAL SAFETY DATA SHEET

PHOTOFRIN® porfimer sodium

AMERICAN HOME PRODUCTS CORPORATION
LEDERLE LABORATORIES
MIDDLETOWN ROAD
PEARL RIVER, NY 10965
EMERGENCY TELEPHONE: 914-732-5000
CHEMTREC FOR CHEMICAL EMERGENCIES: 800-424-9300

MSDS No.: 184.116-02
Supersedes: 184.116-01
DATE: 06/09/95

1. PRODUCT and COMPANY IDENTIFICATION

PRODUCT NAME: PHOTOFRIN® porfimer sodium

USE/SIZE....: Photosensitizing agent for photodynamic therapy

PRODUCT No..: MRD Formulations (CL 184.116)

CAS No.....: [87806-31-3]

SYNONYMS....: Polyporphrin oligomer containing ester and ether linkage; PHOTOFRIN® II; CL 184.116.

TRADE NAMES.: PHOTOFRIN® porfimer sodium

2. COMPOSITION/INFORMATION ON INGREDIENTS

No.	INGREDIENT NAME/SYNONYMS	CAS No.	% WEIGHT
1.	Porfimer sodium	[87806-31-3]	100

3. HAZARDOUS IDENTIFICATION

WARNING! THE TOXICOLOGICAL PROPERTIES OF THIS EXPERIMENTAL MATERIAL ARE NOT KNOWN AT PRESENT.
HANDLE WITH EXTREME CARE.
MAY BE PHOTOTOXIC.
MAY CAUSE EYE AND SKIN IRRITATION, ESPECIALLY UNDER BRIGHTLY LIT CONDITIONS.

3. HAZARDOUS IDENTIFICATION (CONTINUED...)

POTENTIAL HEALTH EFFECTS:

SKIN.....: May cause skin irritation under brightly lit conditions.
INGESTION: None known or expected.
EYE.....: May cause severe eye irritation under brightly lit conditions.
INHALATION: None known or expected.

TARGET ORGAN EFFECTS (SUBCHRONIC/CHRONIC):

Blood and blood forming systems, liver, skin, spleen, bile duct, and adrenal glands (based on animal data).

CARCINOGENIC EFFECTS:

No data applicable.

REPRODUCTIVE/TERATOGENIC EFFECTS:

No data applicable.

CARCINOGENICITY STATUS:

Not listed in (NTP), (IARC), or (OSHA).

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE:

None known.

4. FIRST AID MEASURES

INHALATION: Remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Call a physician.

INGESTION: Do not induce vomiting except as directed by medical personnel. Never give anything by mouth to an unconscious person. Never induce vomiting in an unconscious person. Call a physician.

SKIN.....: Promptly wash with soap and cool running water. Remove contaminated clothing. Contaminated clothing should be washed before reuse. Contact a physician if irritation occurs.

EYES.....: Immediately flush eyes with plenty of cool, low-pressure water for at least 20 minutes. Contact a physician if irritation occurs. Remain in subdued light until examined by medical personnel.

5. FIRE FIGHTING MEASURES

FLASH POINT: N/A METHOD: N/A

AUTOIGNITION TEMP.: N/A

FLAMMABILITY LIMITS:
LOWER: N/A
UPPER: N/A

UNUSUAL FIRE AND EXPLOSION HAZARDS:
Toxic emissions may be given off in a fire. See decomposition products in section 10-Stability and Reactivity.

COMMON EXTINGUISHING METHODS:
Water, Carbon dioxide, Dry chemical, Foam.

FIRE FIGHTING PROCEDURES:
Wear NIOSH/MSHA approved positive pressure, self contained breathing apparatus and full protective turn out gear. Use caution in approaching fire. Use water to keep fire exposed containers cool.

6. ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED:
Review Section 3-Hazards Identification, and Section 8-Exposure Controls/Personal Protection before proceeding with the clean up. Shut off the source of spill or leak if it is safe to do so. Scoop or shovel spilled material into a suitable open head drum. Secure the drum, cover and move; clean spill area thoroughly.

TREATMENT AND DISPOSAL:
Decontaminate or dispose of all protective clothing and equipment. Dispose of in accordance with recommendations in section 13-Disposal Considerations.

REPORTING REQUIREMENTS:
The United States Environmental Protection Agency (USEPA) has not established a Reportable Quantity (RQ) for releases of this material. State and Local regulations vary and may impose additional reporting requirements.

7. HANDLING AND STORAGE

Maintain good housekeeping and personal hygiene procedures.

Aqueous solutions must be stored at or BELOW 20°C.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

EXPOSURE GUIDELINES:

INGREDIENT NAME	OSHA PEL/STEL	ACGIH TLV/STEL	AHPC-TWA
Porfimer Sodium	Not established	Not established	Not established

Continued.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION (CONTINUED...)

VENTILATION:
Use closed-system handling, laboratory bench hood or local exhaust ventilation to control dust or mist.

RESPIRATORY PROTECTION:
When engineering controls are not adequate to contain dust/mist, wear an approved air-purifying respirator with high-efficiency cartridges or a supplied-air respirator.

PROTECTIVE GLOVES:
Rubber gloves and long sleeves should be worn to prevent contact with the skin.

EYE PROTECTION:
The use of Safety Glasses/Goggles are required.

OTHER PROTECTIVE MEASURES:
Minimize excess handling. Keep container closed when not in use. Wash hands, face and exposed body parts at lunch and breaks, and at end of shift.

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AND ODOR: Dark red to reddish-brown cake or crystalline, lyophilized powder. Aqueous solutions are dark red to reddish-brown and practically opaque.

MELTING POINT: Decomposes (color change to black at 225-240°C; did not melt at up to 300°C)

BOILING POINT: 964°C

SPECIFIC GRAVITY/DENSITY: No data available

VAPOR DENSITY: Not applicable

VAPOR PRESSURE: $\leq 2 \times 10^{-11}$ torr @ 20°C

SOLUBILITY:
WATER.....: Soluble to greater than 25 mg/ml at neutral pH; precipitates out of solution when pH is lowered to < 5.
OTHER SOLVENTS: No data available

DECOMPOSITION TEMPERATURE: No data available; color change to black at 225-240°C; did not melt at up to 300°C.

VISCOSITY: Not applicable

pH: 7.2-7.9 (aqueous solution, appx. 13-18 mg/ml)
7.0-8.1 (lyophl. powder reconstituted to 2.5 mg/ml in 5% dextrose in water)

10. STABILITY AND REACTIVITY

STABILITY: Lyophilized powder will retain potency at room temperature (15-25°C) for 18 months. Aqueous solutions will lose potency at room temperature; but are stable for > 30 months at - 20°C.

POLYMERIZATION: Will not occur.

HAZARDOUS DECOMPOSITION PRODUCTS: Emits toxic fumes of CO, CO_2 and NO_x.

CONDITIONS TO AVOID.....: Lyophilized powder: N/A
Aqueous solutions.: Temperatures > - 20°C

INCOMPATIBLE MATERIALS.....: No data available

11. TOXICOLOGICAL INFORMATION

ACUTE/SUBCHRONIC/CHRONIC DATA:

PHOTOFRIN was not an eye or skin irritant in the standard Draize test (no attempt to evaluate the effect of bright light on this protocol was made). There are no acute LD50 data available for PHOTOFRIN by industrially-relevant routes of exposure.

When hematoporphyrin derivative (a less purified version of PHOTOFRIN) was administered intraperitoneally (IP) to dark-housed mice, a 24-hr LD50 of 275 mg/kg was reported; the corresponding LD50 for PHOTOFRIN was 130 mg/kg IP. If mice were exposed to a low level of light for 5 hours after IP administration of the compound, the LD50's dropped to 7.5 and 4 mg/kg for the hematoporphyrin derivative and PHOTOFRIN respectively. In mice exposed to a 12-hr cycle of low light (2.5-14 footcandles (ft-c) for 14 days, one of 10 animals died after a 125 mg/kg intravenous (IV) injection of PHOTOFRIN. Reddening and swelling of the skin and other signs of toxicity were seen at doses $\geq$ 50 mg/kg (IV); 25 mg/kg was a no-effect level. Under brightly lit conditions (120 ft-c for 3 hr, then 4-19 ft-c on a 12-hr cycle), redness, swelling, and/or other signs of phototoxicity were observed at all levels down to 4.8 mg/kg PHOTOFRIN IV. Under these brightly-lit conditions, the LD50 was between 25 and 50 mg/kg IV. In both the IP and IV studies, death was attributed to a shock-like syndrome. Acute studies in rats gave similar light- and dose-related phototoxic effects.

In repeat-dose intravenous studies of PHOTOFRIN® porfimer sodium in rats under normal laboratory lighting conditions, effects were seen in the blood and blood forming systems, the liver, spleen, and bile duct (places where normal porphyrins are accumulated and/or used). These effects were seen to be reversible when administration of PHOTOFRIN was stopped. In subchronic studies in dogs, effects were seen in the blood and blood forming systems, the liver, spleen, and adrenal glands (a recovery phase was not included in the dog study). No studies of the effect of long-term administration with bright light have been conducted.

CARCINOGENIC EFFECTS DATA:

No long-term toxicity studies have been conducted in laboratory animals.

Continued...

11. TOXICOLOGICAL INFORMATION (CONTINUED...)

MUTAGENIC EFFECTS DATA:

PHOTOFRIN was negative with and without light in five different *in vitro* test systems (Ames test, CHO/HGRPT mammalian point mutation assay, Na^+/K^+ ATPase mammalian point mutation, cell transformation and *in vitro* cytogenetics). It was also negative in the mouse micronucleus assay, an *in vivo* test. PHOTOFRIN was marginally positive in one *in vitro* test system (sister chromatid exchange (SCE)), but only in the presence of light. The less purified preparation (hematoporphyrin derivative) is reported in the literature to have caused an increase in the number of DNA strand breaks in bacteria and mammalian cells *in vitro* with light activation. The hematoporphyrin derivative with light activation also produced increases in chromosomal aberrations and weak induction of sister chromatid exchanges.

REPRODUCTIVE/TERATOGENIC EFFECTS DATA:

While PHOTOFRIN was toxic to pregnant rats and rabbits and their offspring (increased fetal resorptions and lowered fetal body weight), it was not teratogenic (did not cause birth defects).

12. ECOLOGICAL INFORMATION

ECOTOXICOLOGICAL INFORMATION:

n-OCTANOL/WATER Partition Coefficient (P_{ow}) of PHOTOFRIN at 24°C was as follows:

pH	P_{ow}	Log P_{ow}
7.0	0.031 ± 0.001	-1.5 ± 0.2
9.0	0.006 ± 0.002	-2.3 ± 0.2

Microbial Inhibition: Photofrin was evaluated for potential inhibitory effects on the growth of pure cultures of bacteria, fungi, and blue-green algae. No inhibition was observed for the test organisms at any of the concentrations (3.91, 15.6, 62.5, 250, and 1000 mg/l) of PHOTOFRIN® porfimer sodium, under the study conditions utilized.

Environmental Concentration Lethal to 50%: The no observed effect level (NOEL) in *Daphnia magna* is 994 mg/l at 24 and 48 hr which classifies PHOTOFRIN® porfimer sodium as practically non-toxic, under the study conditions utilized.

CHEMICAL FATE INFORMATION...: No data available.

13. DISPOSAL CONSIDERATIONS

DISPOSAL RECOMMENDATIONS:

Dispose of in accordance with all Federal, State, and local regulations. Incineration at a permitted facility is recommended.

RCRA WASTE #.....:

This is not a RCRA regulated hazardous waste.

14. TRANSPORT INFORMATION

U.S. DEPARTMENT OF TRANSPORTATION (DOT).....: Non-regulated.

INTERNATIONAL AIR TRANSPORT ASSOCIATION (IATA): Non-regulated.

15. REGULATORY INFORMATION

USEPA: Not regulated.

OSHA: OSHA has not developed a Permissible Exposure Limit (PEL) for Porfimer Sodium (see Section 8).

SARA TITLE III: Not Applicable.

16. OTHER INFORMATION

HAZARD RATINGS*:

NFPA:		HMIS:	
Health.....:	3	Health.....:	3
Flammability...:	0	Flammability...:	0
Reactivity.....:	0	Reactivity.....:	0
Special Hazards:	Phototoxic	Special Hazards:	Phototoxic

*A hazard ratings has not been developed by NFPA or HMIS for this product. The hazard ratings provided in this MSDS are based on NFPA and HMIS hazard evaluation criteria, as well as, professional judgment. This information is intended solely for the use of individuals trained in these hazard rating systems.

PREPARATION AND REVISION INFORMATION

Preparer.....: Hesham M. Soliman/Scientific Consultant (Toxicologist)
Approver.....: S. Rera/Certified Industrial Hygienist/Safety Engineer
A. Moran/Director Safety Services

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: May 17, 1994

From: Asoke Mukherjee Ph.D., HFD-102/HFD-007

Through: Phillip G. Vincent Ph.D., HFD-102

Subject: EA for Photofrin, NDA 20-451

To: Paul F. Zimmerman, HFD-150

The initial review for environmental assessment of the above mentioned NDA has been completed. Following recommendations and comments have been suggested by the reviewer:

Although Photofrin has been granted an orphan drug status, some more data on the fate and effect of Photofrin are necessary for environmental safety as indicated in this memo. The sponsor should be reminded that EA document is available to the public under freedom of information. Therefore any proprietary information in the EA submission should be documented as confidential appendices. Specific comments are as follows:

For item #3

1. Building #, floor, Room # and addresses for Pearl River, New York and Carolina, Puerto Rico sites should be provided as manufacturing sites.

For item #4

2. Drug product from rejected and returned batches of Photofrin should be separated from the glass containers. Glass containers and other packaging materials should be disposed separately. Expired and rejected drug products should be incinerated at an approved facilities.

Provide copies of certificates and permits from local, state and federal authorities for solid, liquid and atmospheric emission at each manufacturing sites. If any permissible limits for the environment is set for the drug substance and materials used in the manufacturing process, that need to be indicated for this item for the purpose of compliance.

For item #6

3. pH of the plant washing should be determined before its discharge to the waste water stream since solubility of Photofrin is dependent on pH. Provide permits from local, state and federal authorities on total BOD allowed to discharge from the plant. Indicate whether manufacturing of Photofrin will affect total permissible BOD at each manufacturing site.

For item #7

4. P_{ow} at pH 5 should be determined for predicting its accumulation in aquatic species.

For item #8

5. Safe levels of photofrin and hematoporphyrin in the rat and mouse tissues at which no organ system toxicity is observed need to be determined after subchronic administration of the drug by i.v. route. Animals should be exposed to light for optimizing its toxicity. Also provide study reports for the repeat dose i.v toxicity in rats and subchronic toxicity in dogs.

Photodegradation of aqueous solution of Photofrin need to be examined.

For item #9

6. How many batches of Photofrin are expected to be manufactured per year. Provide a list of packaging materials, chemicals and equipments to justify that endangered species would not be affected.

For item #10

7. The sponsor need to propose a plan for minimizing light exposure in the manufacturing areas so as to avoid photodegradation and phototoxicity to Photofrin.

For item #13

8. The sponsor should indicate the date when the EA certificate was signed.

Endorsements:

HFD-102/007 Asoke Mukherjee Ph.D.
Pharmacologist

HFD-102/ P.G. Vincent

CC: Original NDA 20-451
EA file
Division File/ HFD-150
Supervisory Chemist/ HFD-150

20451E00.LAM

F/T by AM

HFD/150 P ZIMMERMAN
" J JOHNSON
" J BLUMENSTEIN

Eva Tolgyesi 1/23/95

REQUEST FOR TRADEMARK REVIEW #410

TO: Labeling and Nomenclature Committee
Attention: Yana Mille, Chair, HFD-638, MPN2

FROM: Division of Oncology and Pulmonary Drugs HFD-150
Attention: John M. Schwab Phone: 594-5711

DATE: 1/23/95

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Photofrin NDA/~~ANDA~~# 20-451

Established name, incl. dosage form: Porfimer sodium (sterile, freeze-dried cake or powder for injection)

Other trademarks by the same firm for companion products:
N/A

Indications for use (may be a summary if proposed statement is lengthy):
Antineoplastic: Photofrin is a photosensitizing drug that is used for photodynamic therapy of esophageal cancer. It is used in conjunction with a device that delivers laser energy directly to the affected region.

Initial comments (concerns, observations, etc.) from the submitter:
N/A

Tradenames that sound somewhat similar: Photoplex; Fotostar

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: 451
NDA 20-~~514~~
HFD-150 Division File
HFD-150/Review Chemist/JSchwab
HFD-150/ETolgyesi
HFD-150/CSO/PZimmerman
" /Y Hasch

Consult #410 (HFD-150)

PHOTOFRIN

Porfimer Sodium for Injection

A review did not reveal any names which look or sound similar to the proposed name other than the two names identified by the submitter: Photoplex and Fototar. Due to differences in dosage forms(topical vs. injectable), the Committee does not believe there is a significant risk of confusion involving these product names.

The Committee has no reason to find the proposed name unacceptable.

CDER Labeling and Nomenclature Committee

Yana Ruth Mills, Chair 3/15/95

cc:

Orig NDA
Division File
HFD-150/PZimmerman
" /J Schmidt
" /E Tolgyesi
" /Y Hsieh

memo

Zimmerman

MEMORANDUM OF MEETING

DATE: October 31, 1995 **TIME:** 10-11:30am

PLACE: conference room G

DRUG: Photofrin (porfimer sodium)

NDA: 20-451

SPONSOR: QLT

PARTICIPANTS:

FDA: Dr. Del.ap, Dr. Williams, Dr. Wood, Dr. Hsieh, Dr. McGuinn, Mr. Zimmerman, CSO.

SPONSOR: QLT: Elizabeth Waterfield, Michael Pastel, Ethan Sternbero Alexandra Mancini, Lou Gura, Yua-Kwan Ho, David Dolphin, Stephanie Rais.

SUBJECT: Meeting requested by sponsor to discuss the sponsor's proposed response to the approvable letter chemistry deficiencies.

BACKGROUND INFORMATION:

September 13, 1995 meeting package request with background information.
October 24, 1995 Position Overview facsimile transmission (9 pages).
Overheads provided at the meeting.

SUMMARY/ACTION ITEMS:

- Regarding the capillary electrophoresis method, the Dr.s Wood and Hsieh agreed, based on the data presented for 3 batches of drug product, that this method may provide an adequate fingerprint of the drug. The sponsor was encouraged to continue tc develop this method for product release and for stability study as well. Additional lots should be examined by the CE method and the results submitted to the Agency. Analysis data should include date of manufacture and storage conditions of the sample lots. The sponsor will propose criteria for pass/fail, based on test results.

- Dr.s Wood and Hsieh stated that they were unable to find any reference to an apparent correlation between adverse events and olefinic trimers and tetramers. For this reason, it was agreed that the NMR determination of the olefins for product release could be dropped. The BIHPLC will be used as an

appropriate additional stability-indicating method but will not, at this point, replace the curent bioassay.

- Based on the data presented, Dr.s Wood and Hsieh accepted the proposed modified specifications for hematoporphorin dihydrchloride and hematoporphorin diacetate and the proposed reaction condition ranges for the manufacture of hematoporphorin diacetate.

- It was agreed that QLT will submit, as soon as possible, detetiled information on the specifications and analytical methods to be used for the drug substance (and intermediates), the drug prcduct, and for the stability studies. For the capillary electoophoresis (CE) assay method for the drug product, for which additiaonal data is needed to establish appropriate specifications for product release and stability studies, specific time frames will be set by the applicant for submission of this information to the FDA.

cc:
Orig NDA
Div File
HFD-150/YHsieh
HFD-150/RWood
HFD-150/DMcGuinn
HFD-150/PZimmerman
HFD-150/GWilliams
FT by Zimmerman/11-21-95
Reviewed and revised by Dr. Hsieh and Wood.

MINUTES OF MEETING

DATE: October 8, 1992

DAY: Thursday

TIME: 9-11am

PLACE: Conference room H

SUBJECT: pre-NDA meeting

DRUG: porfimer sodium (photofrin)

IND:

SPONSOR: Lederle Laboratories Division
American Cyanamid Company

PARTICIPANTS:

FDA: Dr. Burke, Dr. Johnson, Dr. Williams, Dr. Hong (ODAC member attended only the pre-meeting by speaker phone), Mr. Felten (ODE), Dr. Gnecco, Dr. Rahman, Mr. Zimmerman, CSO.

SPONSOR: Dr. Desjardins, Dr. Birkofer, Dr. Dugan, Dr. Koury, Dr. Levy, Ms. Welch, Mr. Gura, Dr. Crawford

---

The sponsor's claim for partially obstructed esophageal cancer and the corresponding study comparing PDT to YAG laser therapy in a randomized study were discussed. The sponsor noted time to treatment failure (TTF) as the primary endpoint. The definition of TTF was discussed. The agency noted that the primary endpoint should analyze for local factors only and should address if the patient can achieve swallowing and if so, for how long. Analysis of the other factors can be made separately. The submission should describe how YAG therapy is used and how effective it is in this setting.

The sponsor's claim for completely obstructed esophageal cancer and the corresponding open label, non-comparative study were discussed. the sponsor noted that 19 patients have been treated. 80% have had a reduction of disease by grade 1 or greater and the median duration of response is about 30 days. The agency noted that the dysphagia grade baseline score as submitted at week one should also be submitted for the one month follow-up. Weekly scores should be submitted if available. The case report forms for all patients should be submitted. The determination of the porfimer dose and corresponding laser exposure time and power should also be addressed. In addition, any clear prognostic

factors not to treat and drug interactions with prior chemotherapy, radiation, etc. should be determined using the whole porfimer database.

The sponsor suggested submitting safety data for only local toxicity in the original submission and submitting the rest of the safety data (including ocular toxicity) at the 4 month update. The agency noted that the above safety data would be needed for review much earlier than the scheduled 4 month update. In addition, the agency recommended that the sponsor meet with the chemistry, pharm-tox and biopharm reviewers soon so that the planned submission can be discussed and organized. The possibility of presubmitting CMC was suggested.

The sponsor noted that they plan to submit the NDA in January 1993. However, after discussing the safety data and chemistry submission the sponsor indicated that the date may be moved back.

The sponsor presented the proposed plan for submitting a supplement (in fall of 1993) for refractory transitional cell carcinoma in situ (CIS) of the urinary bladder. The study currently has 22 eligible patients and demonstrates a 55% CR rate with a median duration of about 1 year. Patients must have failed two courses of intravesical therapy and receive PDT as an alternative to cystectomy. In addition to this study there are literature reports of three trials, which have 26/49 eligible patients who had a CR rate of 47%, to be used as supportive data. The sponsor noted that the quality of the data in these trials is poor as is follow up and toxicity data. The agency noted that it would be important to identify risk factors such as prior treatment and to address bladder contractures that have been reported.

Regarding the device it was noted that two PMAs would be submitted in the NDA. One for the laser and one for the fiber optics. The labeling should discuss the specific laser and specific optics.

There was discussion concerning the sponsor's plan to develop PDT in superficial papillary bladder disease that has failed one intravesical therapy. The sponsor proposed reducing the dose of porfimer to 1.5 mg at 15 joules to reduce toxicity (bladder contracture). The agency noted that the safety of the proposed dose must be established before doing this study. Regarding endpoints the agency noted that preventing recurrence would require a controlled study. Delaying recurrence of Ta Grade 1 tumors is highly unlikely to be sufficient basis for approval unless the result is spectacular or the treatment much less complicated and benign than this one. For phototherapy a decrease in progression in stage or grade will be necessary for

approval. The agency also suggested that if there was no option except cystectomy then a non-controlled study may be acceptable.

The agency re-emphasized the need to address chemistry, pharm-tox and biopharm issues soon.

Paul F. Zimmerman
Oncology Drug Products

cc:
Orig IND
Div File
HFD-150/JRJohnson
HFD-150/GWilliams
HFD-150/PZimmerman/10-9-92/10-15-92
HFD-150/JDeGeorge
HFD-150/JBlumenstein
HFD-713/CGnecco
HFD-426/ARahman
HFZ-410/RFelten
R/D init by GWilliams/10-13-92
JRJohnson/10-14-92

MINUTES OF MEETING

DATE: October 21, 1993

DAY: Thursday

TIME: 9:30-11am

PLACE: Conference Room 200S/ Woodmont building

SUBJECT: pre-NDA chemistry/pharmacology issues

DRUG: PHOTOFRIN (porfimer sodium) for Injection

IND:

SPONSOR: Lederle

PARTICIPANTS:

FDA: Dr. Burke, Dr. Johnson, Dr. DeGeorge, Dr. Goheer, Dr. Blumenstein, Dr. Tolgyesi, Dr. Haggerty (Orphan Drugs), Mr. Zimmerman, CSO.

SPONSOR: see package

The purpose of the meeting was to discuss chemistry issues related to the proposed NDA filing such as, characterization of the drug substance, analytical methods including the bioassay, and stability. Correlation of these factors to safety and efficacy would also be discussed.

The sponsor briefly presented background information concerning photodynamic therapy (PDT) and presented the structures of the potential oligomers and isomers of hematoporphyrin and noted that they plan to file the NDA late December this year (1993).

After the sponsor presented analytical methods there was discussion about characterization of the drug. The Agency acknowledged that the drug is a complex mixture of monomers, oligomers stereo- and regioisomers. More information is needed concerning the oligomer ratio in representative batches of the drug product and the biological activity of specific oligomers. The sponsor should demonstrate the ability to manufacture the drug product with batch to batch reproducibility. The Agency noted that the frozen and lyophilized dosage forms of the drug product had different adverse event profiles although differences in batch characteristics have not been identified using the current regulatory analytical methodology. The sponsor presented information via overhead identifying oligomer ratios in some batches. Dr. Blumenstein noted that the current level of product characterization and control is not sufficient. Minimally, oligomer ratios should be included into the regulatory release specifications for PHOTOFRIN for Injection.

There was discussion about the submitted bioassay. The Sponsor stated that the bioassay is a biological use test with low sensitivity and an endpoint of tumor resolution. A test is needed that will be sensitive enough to identify super-potent batches as well as impotent batches in relation to clinically relevant changes in dose response. The Agency asked if there is an animal test to assess safety. The sponsor noted that a foot edema test might be applicable. The agency suggested to investigate dose-response relationship in tumor bearing animals, and skin test to evaluate the toxicity and efficacy of different batches of photofrin.

Regarding stability, the sponsor presented test data for storage at 23°C for up to 30 months. Dr. Blumenstein noted that oligomer ratio information over the claimed expiry period is needed. Additionally, the 23°C storage temperature is not an appropriate storage condition and 30°C or 25°C should be used. Data from 30°C storage may be used to support labeling at 25°C. Labeling for storage up to 23°C would not be appropriate. The sponsor inquired if the NDA should be filed at this point. The Agency suggested that additional work as discussed is needed.

The sponsor presented information via overhead projector comparing adverse events from frozen drug product vs lyophilized drug product vs YAG in patients with esophageal cancer. It was noted that the change to lyophilized drug product occurred in January 1990. There was discussion about the adverse events including anemia (local blood loss) atrial fibrillation and pleural effusion. The Agency noted that the presented adverse events appeared to be worse for the lyophilized drug product than for the previously used frozen concentrate formulation.

The sponsor was requested to submit copies of the overheads that were used during the meeting.

cc:
Orig IND
Div File
HFD-150/JRJohnson
HFD-150/GWilliams
HFD-150/PZimmerman/10-21-92/11-8-93
HFD-150/JDeGeorge
HFD-150/JBlumenstein
HFD-15013/ETolgyesi
HFD-150/AGoheer
R/D init by GWilliams/11-3-93
JRJohnson/11-3-93
AGoheer/10-22-93
JDeGeorge/10-22-93
ETolgyesi/10-22-93
JBlumenstein/10-22-93

MINUTES OF MEETING

DATE: July 25, 1994

DAY: Monday

TIME: 11am

PLACE: 6002 Woodmont

SUBJECT: 90 day conference

DRUG: porfimer sodium (photofrin)

NDA: 20-451

SPONSOR: QLT and Lederle Laboratories Division
American Cyanamid Company

PARTICIPANTS:

FDA: Dr. Blumenstein, Dr. Lowenthal, Dr. McGuinn, Mr. Zimmerman, CSO.

SPONSOR: Dr. Mancini, Dr. Dukart, Dr. Gura, Dr. Lawter, Dr. Pastel, Dr. Johnson

---

The purpose of the meeting was to provide the sponsor with status of the review of the NDA and to transmit deficiencies that had not been previously communicated.

There was discussion about what information is available on the different lots (and manufacturing schemes, of photofrin used for preclinical studies. There is no information in the application on acute toxicity or histopathology for scheme drug. There was discussion about the ratio for the different schemes. The Agency noted that the application indicated that this ratio had been inverted in the different schemes (formulations). The sponsor stated that in all schemes the has been the minor component ranging from % with the later being the percentage for formulation in the proposed application. An acute toxicity study focusing on histopathology and differences in metabolism may be needed to link scheme and scheme

The Agency noted that there has been frequent communication with the sponsor regarding different aspects of the chemistry review. There will be a deficiency letter issued. However, the requested DMFs for the starting substance will need to be reviewed before the letter can be issued. The sponsor stated that the DMFs should be available this week (7-25-94).

There was brief discussion about the bioassay. The Agency noted that we are reasonable comfortable with the assay; however, full review is pending. The sponsor will provide bioassay results from the other schemes for comparison.

There was discussion about the apparent-molecular weight distribution changes due to the methods of manufacture for the scheme and scheme formulations.

Regarding the bioassay, it was noted that the stability study uses the old bioassay and the release testing uses the new bioassay. The use of the old bioassay may limit the usefulness of the stability studies

There was brief discussion about the possibility of radiolabeling photofrin. The sponsor noted that attempt had been made to do this but was not successful .

cc:
Orig IND
Div File
HFD-150/PZimmerman
HFD-150/RLowenthal
HFD-150/JBlumenstein
HFD-150/WMcGuinn
HFD-150/GWilliams
HFD-150/JRJohnson
HFD-150/JDeGeorge

R/D init by WMcGuinn/7-27-94
RLowenthal/7-27-94
JBlumenstein/8-2-94

MINUTES OF MEETING

DATE: January 12, 1995

DAY: Thursday

TIME: 1-2pm

PLACE: 6002 Woodmont

SUBJECT: Industry meeting

DRUG: porfimer sodium (photofrin)

NDA: 20-451

SPONSOR: QLT and Lederle Laboratories Division
American Cyanamid Company

PARTICIPANTS:

FDA: Dr. Temple, Dr. Justice, Dr. Williams, Dr. Tolgyesi, Dr. Schwab, Dr. DeGeorge, Dr. McGuinn, Dr. Koutsoukos, Dr. Mehta, Dr. Rahman, Mr. Felten, Mr. Zimmerman, CSO.

SPONSOR: QLT -Ms. Mancini, Dr. Sternberg, Dr. Wallis, Dr. Chase. American Home Products- Dr. Gura, Dr. Freitag, Mr. Pastel, Dr. Lawter.

The purpose of the meeting was to allow interaction with the sponsor to develop a strategy for progressing toward marketing this new drug product.

The sponsor agreed to do a Phase 4 study in patients with the agreed upon indication which will be specified and will include patients with completely obstructed esophageal cancer and patients with certain types of partially obstructed esophageal

cancer.

The sponsor provided a commitment to do a Phase 4 toxicology study using the appropriate drug product. The details of the study will be forthcoming.

There was discussion about pharmacokinetics. The sponsor agreed to conduct Phase 4 studies to characterize the pharmacokinetics of Photofrin including pharmacokinetics in patients with hepatic dysfunction. The sponsor stated that they will soon respond to the requests from the Biopharm review contained in the fax dated December 7, 1994.

There was considerable discussion about the chemistry, manufacturing and controls. It was agreed the sponsor needs to demonstrate that the manufacturing process is under control, i.e., that there is no significant batch-to-batch variation and thus the batches used in the pivotal clinical study (utilizing Scheme material) are substantially equivalent in chemical composition and biological activity to those produced for commercial distribution. For this objective adequate methodology

is needed to characterize the batches for content of monomeric impurities, oligomer content and size distribution, hydroxyethyl and vinyl functional groups, linkage ratios, etc. There was discussion about developing a combination of analytical methods such as HPLC and FAB mass spec to provide a chemical "fingerprint".

It was also agreed that storage stability must be demonstrated so that an expiration dating period can be assigned. The sponsor noted that reserve batches are available for comparison.

The firm agreed to provide data pertaining to "superpotency".

The firm also noted that there are retention samples available for comparing the clinical trial material with the new batches.

With specific reference to the chemistry information request letter dated November 18, 1994, the sponsor stated that they expect to provide a complete response by mid March 1995. Responses to substantive issues may be submitted earlier.

cc:
Orig. NDA
Div File
HFD-150/Grant Williams
HFD-150/Eva Tolgyesi
HFD-150/John Schwab
HFD-150/Joe DeGeorge
HFD-150/David McGuinn
HFD-426/Mehul Mehta
HFD-426/Atik Rahman
HFD-713/Steve Wilson
HFD-713/AKoutsoukos
HFZ-410/Richard Felten
HFD-150/Paul Zimmerman
HFD-150/DPease
HFD-160/PCooney
HFD-160/CVincent
HFD-102/PVincent
HFD-344/GTurner

R/D init by MMehta/
WMcGuinn/
JDeGeorge/
JSchwab/
ETolgyesi/
GWilliams/
RJustice/

ODAC mtg
9/12/94
minutes

Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES
ONCOLOGIC DRUGS ADVISORY COMMITTEE

Meeting #42: September 12, 1994
Parklawn Building, Conference Room E
Rockville, Maryland

Members Present
Charles Schiffer, M.D., chair
Kim Margolin, M.D.
Daniel Ihde, M.D.
James Ingle, M.D.
Paul Bunn, M.D.
Judith Ochs, M.D.
Albert Siu, M.D.
Richard Gelber, Ph.D.
George Omura, M.D.
Sandra Swain, M.D.

Members Absent
Arlene Forastiere, M.D.

FDA Participants
Gregory Burke, M.D., Ph.D.
Robert Temple, M.D.
Grant Williams, M.D.
Richard Felten

Consultants
Norman Nishioka, M.D.
Mary McGrath, M.D.

Executive Secretary
Adele Seifried, M.S.

These summary minutes for the September 12, 1994, meeting of the Oncologic Drugs Advisory Committee were approved on DEC 12 1994.

I certify that I attended the September 12, 1994, meeting of the Oncologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

Adele S. Seifried, M.S.
Executive Secretary

Charles Schiffer, M.D.
Chairman

This meeting was held in open session in the morning and closed session in the afternoon. The open session was attended by approximately 150 persons. Background provided to the committee members included summary packages from the sponsor on Photofrin, and two medical reviews and a statistical review from FDA. The meeting began at 8:05 a.m., on September 12, 1994, with Dr. Charles Schiffer, Chairman, presiding.

Conflict of Interest

The Conflict of Interest statement noted that there were no conflicts of interest relative to the agenda.

Open Public Hearing

There were no requests to speak at the open public hearing, so the meeting moved to the next agenda item.

Agenda

The meeting agenda included discussion of NDA 20-451, Photofrin® (Sterile Porfimer Sodium, QLT Phototherapeutics, Inc.), "for the reduction of obstruction and palliation of dysphagia in patients with completely or partially obstructing esophageal cancer."

Issue #1 -Review of NDA 20-451 - Photofrin

QLT PRESENTATION

Alexandra Mancini gave the overview, describing photodynamic therapy (PDT) as the use of an intravenous drug, a light source (a red light produced by a laser source), and a light delivery system. Dr. Julia Levy presented a brief overview of the pharmacologic mechanism of action of the drug, explaining that PDT is used to activate the drug on day three following intravenous administration, because the drug clears more rapidly from normal tissue than it does from tumor tissue and its neovasculature. Dr. Charles Lightdale, one of the leading investigators from both clinical trials, discussed both efficacy and safety data. He stated that most patients with esophageal cancer are incurable and will require palliative therapy. Among the options, dilation lasts only a brief time; stents can plug with food or become overgrown with tumor; thermal methods, such as the YAG laser, are associated with perforation; and with chemical methods it is difficult to control the diffusion of the sclerosant. Completely obstructed patients are even more difficult to treat. He stated that surgical palliation requires a high degree of technical skill, and comes with a high risk of perforation; that PDT offers potentially the only satisfactory treatment of opening the lumen for palliation of completely obstructed patients. Of the two major endpoints to measure

efficacy, palliation of dysphagia as measured by the change in the dysphagia grade was more important for the patient than was reduction of obstruction as measured by objective tumor response. Three-quarters of the patients with complete obstruction achieved a CR or a PR. PDT is a more diffuse treatment that allows all tumors to be treated, while with YAG it is difficult to treat long tumors, narrow angulated tumors, or those that occur in the cervical esophagus or the esophageal-gastric junction. He concluded that PDT is needed for patients with partially obstructing esophageal cancer and is the only feasible palliative approach for patients with complete obstruction, and that the toxicity is acceptable considering the severity of the disease and the extreme need for palliation.

FDA PRESENTATION:

Richard Felten, from the Center for Devices and Radiological Health (CDRH), briefly reviewed the devices and explained that the devices would only be approved in conjunction with the drug. He stated that CDRH did not have any particular problems with the devices, but would ask for a recommendation from the committee regarding their approvability.

Dr. Grant Williams discussed the different endpoints. The time to recurrence and response duration endpoints were not used. The main endpoint that evolved was symptom palliation. He felt that there was evidence of efficacy, but was concerned with the toxicity.

COMMITTEE DISCUSSION

The two committee reviewers were Dr. Paul Bunn and Dr. Kim Margolin, who led off the discussion of the questions posed by FDA:

Questions on Photofrin:

Q1. In study P 19 of PDT (with Photofrin) vs. ND:YAG laser therapy for partially obstructing esophageal cancer several efficacy endpoints were evaluated:

Response: Objective response as analyzed in the study was primarily based on proof of a 50% increase in luminal diameter.

Change in Dysphagia Grade:
Symptom palliation, as manifested by change in dysphagia grade, was a primary endpoint identified in the protocol.

Time to event endpoints:
Time to Treatment Failure and Time to Palliation Failure were complex time to event endpoints.

Graphical display of Individual patient data:
Subjective evaluation of numerous elements in individual patients were aided by graphical display.

A. For each of the above endpoints address the following points:

i. Is the endpoint an adequate surrogate for efficacy in patients with partially obstructing esophageal cancer?

ii. Is the design and conduct of the trial and quality of the data collected sufficient to allow a reasonable assessment of this endpoint?

Committee Response:

Response: A 50% increase in luminal diameter is an arbitrary, but reasonable measurement. It is difficult to assess, but probably as good of a surrogate endpoint as you can get, other than dysphagia grade. It was suggested that maximum diameter achieved might be a preferable measure.

Change in Dysphagia Grade: This was the primary endpoint, the point of the whole study.

Time to event endpoints: These were nearly useless for this analysis, and difficult to accept as surrogates or endpoints based on the information given in this trial. This could be done in subsequent trials, but a prospective definition of all of the types of failure would need to be given.

Graphical display of Individual patient data: This is useful primarily to the reviewer, and also useful in the palliation setting or when there are mixed results. It would allow a determination of whether there were individuals who were helped.

B. Overall, do the results demonstrate that PDT with photofrin is efficacious in patients with partially obstructing esophageal cancer?

Vote: 12 yes (in a minority of patients, for a limited time); 0 no

Q2. Photofrin should not be approved for patients eligible for YAG laser treatment.

Vote: 6 yes; 6 no.

Q3. Is Photofrin approvable for patients who, in the opinion of their physician, cannot be satisfactorily treated with YAG because of, for example, obstructing lesions or proximal, flat or angulated tumors? Relative toxicities should be shown in the labeling, and post marketing data should be collected.

Vote: 11 yes; 1 no.

Q4. (To clarify the double negative wording of vote #2) How many would be in favor of wide approval of Photofrin for partially obstructing esophageal cancer?

Vote: 5 yes; 7 no.

Q5. Are the devices approvable?

Vote: 12 yes; 0 no.

At 12:35, the open session concluded. After a break for lunch, the Committee met in closed session.

[redacted]