

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-525**

**NDA 20-451/S-012**

**Clinical Pharmacology and Biopharmaceutics  
Review**

**Office of Clinical Pharmacology and Biopharmaceutics Review  
Division of Pharmaceutical Evaluation II**

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**NDA:** 21-525  
**Brand Name:** Photofrin® (Porfimer Sodium) for Injection  
**Generic Name:** Porfimer Sodium  
**Dosage form and Strength:** Lyophilized powder for reconstitution (75 mg/vial)  
**Route of administration:** Intravenous (IV) short-term infusion (3-5 min)  
**Indication:** Ablation of high-grade dysplasia (HGD) in Barrett's esophagus among patients who are not considered to be candidates for esophagectomy  
**Sponsor:** Axcan Scandipharm Inc.  
**Type of submission:** Type 6 NDA (New Indication)  
**Clinical Division:** HFD-180  
**OCPB Division:** HFD-870/DPE II  
**Priority:** Priority  
**Submission date:** 05/31/02  
**OCPB Consult date:** 06/10/02  
**Reviewer:** Tien-Mien Chen, Ph.D.  
**Team leader:** Suresh Doddapaneni, Ph.D.

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**I. Executive Summary**

Photofrin (porfimer sodium) for Injection (75 mg/vial) under NDA 20-451 was approved by the Oncology Division (HFD-150) on 12/27/95 for the following indications:

- 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.
- reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial nonsmall cell lung cancer (NSCLC).
- treatment of microinvasive endobronchial NSCLC in patients for whom surgery and radiotherapy are not indicated.

On 05/31/02, a new NDA 21-525 (Type 6) was submitted for the following new indication:

- The ablation of high-grade dysplasia (HGD) in Barrett's esophagus (BE) among patients who are not considered to be candidates for esophagectomy.

The same dose is proposed using the currently marketed 75 mg/vial, except for minor differences/changes in laser light (device) and timing of illumination. It has been designated an Orphan Drug status (10/19/01). No new PK studies were conducted for Photofrin for Injection to support the new indication. Five recent literature articles published between 1995 and 2001 describing the general pharmacokinetics (PK) of this drug were submitted for review. The results are consistent with those reported previously. No new CPB labeling changes are proposed. Finally, the sponsor will fulfill OCPB Phase IV comment (No. 2) under previous NDA 20-451 as follows:

**“Conduct Phase IV studies to gather further pharmacokinetic (PK), data in patients with hepatic impairments and in patients who have received more than one course of therapy.”**

Recommendation:

Axcan's NDA 21-525 (Photofrin for Inj.) submitted on 05/31/02 seeking the new indication is acceptable from OCPB/DPE II viewpoint provided that the previous labeling changes (under NDA 20-451) as proposed by the Agency dated 12/11/01 regarding PK section (including the results of gender analysis) are incorporated into the labeling.

**“The pharmacokinetics of PHOTOFRIN<sup>®</sup> was also studied in 24 healthy subjects (12 men and 12 women) who received a single dose of 2 mg/kg PHOTOFRIN<sup>®</sup> given via the intravenous route. ~~Serum samples were collected out to 36 days after injection.~~ The serum decay was bi-exponential, with a slow distribution phase and a very long elimination phase that started approximately 24 hours after injection. The elimination half-life was  $415 \pm 104$  hours ( $17 \pm 4.3$  days).  $C_{max}$  was determined to be  $40 \pm 11.6$  mcg/mL and  $AUC_{inf}$  was  $2400 \pm 552$  mcg·hour/mL. Women had lower  $C_{max}$  and higher AUC. The clinical significance of these differences is unknown. Gender had no effect on pharmacokinetic parameters except  $t_{max}$  which was approximately 1.5 hours in women and 0.17 hours in men. At the time of intended photoactivation 40-50 hours after injection, the pharmacokinetic profiles of PHOTOFRIN<sup>®</sup> in men and women were very similar”.**

10/16/02

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD initialed by Suresh Doddapaneni, Ph.D. 10/25/02

FT initialed by Suresh Doddapaneni, Ph.D. 11/04/02

cc: NDA 21-525, HFD-180 (E. Kaminskas, B. Strongin), HFD-870 (T. M. Chen, S. Doddapaneni, J. Hunt, H. Malinowski).

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## III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Photofrin (porfimer sodium) for Injection (75 mg/vial) reviewed under NDA 20-451 was approved by the Oncology Division (HFD-150) previously. The recommended photodynamic therapy (PDT) is a two-stage process requiring administration of both the drug and laser light (device). The first stage of PDT is a short-term intravenous (IV) injection (over 3-5 min) of Photofrin dose of 2 mg/kg for all indications. Illumination with laser light (630 nm) 40-50 hrs following injection with Photofrin, constitutes the second stage of therapy. A second laser light application may be given 96-120 hrs after injection, preceded by gentle debridement or residual tumor. Patients may receive a second course of PDT after the initial therapy with a minimum of 30-day separation between the PDT for esophageal cancer and NSCLC and a minimum of 90-day separation for the HGD in Barrett's esophagus.

For previous NDA 20-451, one pivotal PK study (D73P503) and two supportive studies (Nos. 2 and 4) were reviewed. The approved package insert (PI) states the following information in the PK subsection under the Clinical Pharmacology Section:

**"Following a 2 mg/kg dose of porfimer sodium to 4 male cancer patients, the average peak plasma concentration was  $15 \pm 3$  mcg/mL, the elimination half-life was  $250 \pm 285$  hours, the steady-state volume of distribution was  $0.49 \pm 0.28$  L/kg, and the total plasma clearance was  $0.051 \pm 0.035$  mL/min/kg. The mean plasma concentration at 48 hours was  $2.6 \pm 0.4$  mcg/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 mcg/mL".**

Upon approval, Axcan Scandipharm Inc., agreed to fulfill 5 Phase IV commitments. Commitment No. 2 was related to OCPB, i.e.,

**"Conduct Phase IV studies to gather further pharmacokinetic (PK), data in patients with hepatic impairments and in patients who have received more than one course of therapy. PK will also be characterized in male and female patients".**

The sponsor subsequently conducted PK study PHO PK 001 that included three parts, i.e., 1) to address gender differences in 24 healthy male and female subjects, 2) in subjects with hepatic impairment, and 3) in a multiple-dose setting. However, it was terminated prematurely (Part 1) due to 100 % photosensitivity in those healthy subjects. The study results of the PK data in 24

healthy subjects including proposed labeling changes were submitted to the Agency for review on 05/18/00 and 05/29/01. The above supplements were reviewed by OCPB and the Agency's comments on labeling changes regarding gender analysis were sent to the sponsor on 12/11/01 as shown below:

**"The pharmacokinetics of PHOTOFRIN® was also studied in 24 healthy subjects (12 men and 12 women) who received a single dose of 2 mg/kg PHOTOFRIN ® given via the intravenous route. Serum samples were collected out to 36 days after injection. The serum decay was bi-exponential, with a slow distribution phase and a very long elimination phase that started approximately 24 hours after injection. The elimination half-life was  $415 \pm 104$  hours ( $17 \pm 4.3$  days).  $C_{max}$  was determined to be  $40 \pm 11.6$  mcg/mL and  $AUC_{inf}$  was  $2400 \pm 552$  mcg·hour/mL. Women had lower  $C_{max}$  and higher AUC. The clinical significance of these differences is unknown. Gender had no effect on pharmacokinetic parameters except  $t_{max}$  which was approximately 1.5 hours in women and 0.17 hours in men. At the time of intended photoactivation 40-50 hours after injection, the pharmacokinetic profiles of PHOTOFRIN® in men and women were very similar".**

However, the above proposed labeling changes have not been implemented into the PI of Photofrin for Injection (NDA 20-451 or 21-525). Please see the proposed labeling (Appendix 2; 04/25/02 version) for details.

In the meantime, the sponsor requested an exemption on 05/14/01 for Parts 2 and 3 of the outstanding OCPB Phase IV commitment No. 2. On 12/11/01, the waiver request was reviewed, but not granted by the Agency. On 10/25/02, the sponsor discussed the above outstanding OCPB Phase IV commitment with HFD-150. It was concluded that the sponsor agreed to fulfill the outstanding OCPB Phase IV commitment (hepatic impairment and multiple dosing) and will collect PK data from the proposed clinical trials in cancer patients. Please see Agency's review and letters for more information.

Finally, for this new indication, no new PK studies were conducted. Five current literature articles (between 1995 and 2001) were submitted. The results are consistent with those reported previously. Thus, no new changes describing the general PK information are proposed.

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## VI. Question Based Review

### General Clinical Pharmacology:

1. Does the CPB data support the new indication?

No changes in PK of porfimer in this patient population are expected. Since the same dose is proposed, no new PK studies were conducted. The results from five recently published literature articles describing the general PK showed that 1) porfimer exhibited poly-exponential decay post IV administration, 2) tumor cells tend to show higher intake of drug, 3) in general, it is eliminated more slowly from carcinoma tissue than normal tissue, and 4) dose-limiting toxicity (thrombocytopenia) was seen at 8 mg/kg, but not < 4 mg/kg. These results are consistent with those reported previously.

A pivotal clinical study (No. **PHO BAR-01**) was conducted to determine the efficacy and safety (up to 24 months) of Photofrin for Inj. in this patient population. The drug-drug interaction (DDI) potential with co-administered drugs has not been evaluated. In the above clinical trial, omeprazole was given with Photofrin and safety information is available. However, the sponsor considered that the clinically significant DDI between Photofrin and omeprazole (or proton pump inhibitor products) is unlikely to occur due to differences in their metabolism and elimination.

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## **V. Appendices**

### **Appendix 1**

**Cover Sheet and OCPB Filing/Review Form**

Office of Clinical Pharmacology and Biopharmaceutics  
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-525	Brand Name	Photofrin for Inj.
OCPB Division (I, II, III)	II	Generic Name	Porfimer sodium
Medical Division	GI & Coagulation	Drug Class	A complex mixture of porphyrin oligomers
OCPB Reviewer	Tien-Mien Chen, Ph.D.	Indication(s)	Ablation of High-grade Dysplasia in Barrett's Esophagus
OCPB Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Lyophilized powder
		Dosing Regimen	2 mg/kg given IV over 3-5 min
Date of Submission	05/24/02	Route of Administration	IV
Estimated Due Date of OCPB Review	11/02/02	Sponsor	Axcan Scandipharm/CanReg
Medical Division Due Date	11/04/02	Priority Classification	P
PDUFA Due Date	11/29/02		

**Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	<input type="checkbox"/>	<input type="checkbox"/>	
Tabular Listing of All Human Studies	X	<input type="checkbox"/>	<input type="checkbox"/>	
HPK Summary	X	<input type="checkbox"/>	<input type="checkbox"/>	
Labeling	X	<input type="checkbox"/>	<input type="checkbox"/>	
Reference Bioanalytical and Analytical Methods	X	<input type="checkbox"/>	<input type="checkbox"/>	
<b>I. Clinical Pharmacology</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Mass balance:		0		
Isozyme characterization:		0		
Blood/plasma ratio:		0		
Plasma protein binding:		0		
Pharmacokinetics (e.g., Phase I) -	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Healthy Volunteers -	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
single dose:		4	0	Previously reviewed (2 pivotal + 2 supportive)
multiple dose:		0		
Patients -	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
single dose:		0		
multiple dose:		0		
Dose proportionality -	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Fasting / non-fasting single dose:		0		
fasting / non-fasting multiple dose:		0		
Drug-drug interaction studies -	N/A	<input type="checkbox"/>	<input type="checkbox"/>	
In-vivo effects on primary drug:		0		
In-vivo effects of primary drug:		0		
In-vitro:		0		
Subpopulation studies -	N/A	<input type="checkbox"/>	<input type="checkbox"/>	
ethnicity:		0		
gender:				Analyzed based on # PHO PK 001
pediatrics:		0		
geriatrics:		0		
renal impairment:		0		
hepatic impairment:		0		
PD:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Phase 2:		0		
Phase 3:		0		
PK/PD:	N/A	<input type="checkbox"/>	<input type="checkbox"/>	No PK/PD analysis was done
Phase 1 and/or 2, proof of concept:		0		
Phase 3 clinical trial:		0		
Population Analyses -	N/A	<input type="checkbox"/>	<input type="checkbox"/>	
Data rich:	---	---		
Data sparse:	---	---		

<b>II. Biopharmaceutics</b>	<b>N/A</b>			
Absolute bioavailability:		0		
Relative bioavailability -	<b>N/A</b>	0		
solution as reference:		0		
Alternate formulation as reference:		0		
<b>Bioequivalence studies -</b>	<b>N/A</b>			
traditional design; single / multi dose:		0		
replicate design; single / multi dose:		0		
Food-drug interaction studies:		0		
Dissolution:		0		
(IVIVC):		0		
Bio-wavier request based on BCS		0		
BCS class				
<b>III. Other CPB Studies</b>	<b>X</b>			
Genotype/phenotype studies:		0		
Chronopharmacokinetics		0		
Pediatric development plan		0		
Literature References		5	5	
<b>Total Number of Studies</b>		<b>9</b>	<b>5</b>	
<b>Filability and QBR comments</b>				
	<b>"X" if yes</b>	<b>Comments</b>		
<b>Application filable ?</b>	<b>X</b>	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
<b>Comments sent to firm ? No!</b>	<b>Needs to be sent</b>	Your request for waiver/release from the Phase IV commitment No. 2 under NDA 21-451 (on multiple-dose PK and on PK in patients with hepatic impairment) has not been granted. According to FDA's letter dated 12/11/01, it is recommended that the above comment be addressed in a clinical trial. Therefore, please provide the status update of the above Phase IV comment.		
<b>QBR questions (key issues to be considered)</b>	<b>Do the published articles support the labeling of this NDA?</b>			
<b>Other comments or information not included above</b>	This is a type 6 NDA. Approval is sought for a new indication for a previously approved product (NDA 20-451).			
<b>Primary reviewer Signature and Date</b>	Tien-Mien Chen, Ph.D. 07/09/02			
<b>Secondary reviewer Signature and Date</b>	Suresh Doddapaneni, Ph.D. 07/09/02			

CC: NDA 21-525, HFD-850 (Electronic Entry or Lee), HFD-180 (R. Prizont, B. Strongin), HFD-870 (T. M. Chen, S. Doddapaneni, J. Hunt, H. Malinowski), CDR (Z. Zadeng)

## **Appendix 2**

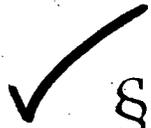
**Proposed Package Insert (Annotated; 04/25/02 version)**

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\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

\_\_\_\_ § 552(b)(5) Deliberative Process



✓ § 552(b)(4) Draft Labeling

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/s/

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Tien-Mien Chen :  
11/5/02 11:12:20 AM  
BIOPHARMACEUTICS

Suresh Doddapaneni  
11/5/02 12:01:40 PM  
BIOPHARMACEUTICS

*Office of Clinical Pharmacology and Biopharmaceutics*  
*New Drug Application Filing and Review Form*

**General Information About the Submission**

	Information		Information
NDA Number	21-525	Brand Name	Photofrin
OCPB Division (I, II, III)	II	Generic Name	Porfimer for Inj.
Medical Division	GI & Coagulation	Drug Class	A complex mixture of porphyrin oligomers
OCPB Reviewer	Tien-Mien Chen, Ph.D.	Indication(s)	Ablation of High-grade Dysplasia in Barrett's Esophagus
OCPB Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Lyophilized powder
		Dosing Regimen	2 mg/kg given IV over 3-5 min
Date of Submission	05/24/02	Route of Administration	IV
Estimated Due Date of OCPB Review	09/30/02	Sponsor	Axcan Scandipharma/CanReg
Medical Division Due Date	10/15/02	Priority Classification	P
PDUFA Due Date	11/29/02		

**Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>	<input checked="" type="checkbox"/>			
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
<b>I. Clinical Pharmacology</b>	<input checked="" type="checkbox"/>			
Mass balance:		0		
Isozyme characterization:		0		
Blood/plasma ratio:		0		
Plasma protein binding:		0		
Pharmacokinetics (e.g., Phase I) -	<input checked="" type="checkbox"/>			
<i>Healthy Volunteers-</i>	<input checked="" type="checkbox"/>			
single dose:		1	0	Previously reviewed # PHO PK 101
multiple dose:		0		
<i>Patients-</i>				
single dose:		0		
multiple dose:		0		
Dose proportionality -				
fasting / non-fasting single dose:		0		
fasting / non-fasting multiple dose:		0		
Drug-drug interaction studies -	<input checked="" type="checkbox"/>			
In-vivo effects on primary drug:		0		
In-vivo effects of primary drug:		0		
In-vitro:		0		
Subpopulation studies -	<input checked="" type="checkbox"/>			
ethnicity:		0		
gender:				Analyzed based on # PHO PK 101
pediatrics:		0		
geriatrics:		0		
renal impairment:		0		
hepatic impairment:		0		

PD:	<b>R</b>	<b>I</b>		
Phase 2:		0		
Phase 3:		0		
PK/PD:	<b>N/A</b>	<b>I</b>		
Phase 1 and/or 2, proof of concept:		0		
Phase 3 clinical trial:		0		
Population Analyses -	<b>N/A</b>			
Data rich:	---	---		
Data sparse:	---	---		
II. Biopharmaceutics	<b>N/A</b>			
Absolute bioavailability:		0		
Relative bioavailability -	<b>N/A</b>	<b>I</b>		
solution as reference:		0		
alternate formulation as reference:		0		
Bioequivalence studies -	<b>N/A</b>	<b>I</b>		
traditional design; single / multi dose:		0		
replicate design; single / multi dose:		0		
Food-drug interaction studies:		0		
Dissolution:		0		
(IVIVC):		0		
Bio-wavier request based on BCS		0		
BCS class				
III. Other CPB Studies	<b>R</b>			
Genotype/phenotype studies:		0		
Chronopharmacokinetics		0		
Pediatric development plan		0		
Literature References		4		
Total Number of Studies		5		
<b>Filability and QBR comments</b>				
	<b>"X" if yes</b>	<b>Comments</b>		
Application filable ?	<b>X</b>	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ? No!	Needs to be sent	Your request for waiver/release from the Phase IV commitment No. 2 under NDA 21-451 (on multiple-dose PK and on PK in patients with hepatic impairment) has <u>not</u> been granted. According to FDA's letter dated 12/11/01, it is recommended that the above comment be addressed in a clinical trial. Therefore, please provide the status update of the above Phase IV comment.		
QBR questions (key issues to be considered)	Do the published articles support the labeling of this NDA?			
Other comments or information not included above	This is a type 6 NDA. Approval is sought for a new indication for a previously approved product (NDA 21-451).  Please see Agency's responses to sponsor's Phase IV Comments in Attachments for details.			
Primary reviewer Signature and Date	Tien-Mien Chen, Ph.D.			
Secondary reviewer Signature and Date	Suresh Doddapaneni, Ph.D.			

CC: NDA 21-525, HFD-850 (Electronic Entry or Lee), HFD-180 (R. Prizont, B. Strongin), HFD-870 (T. M. Chen, S. Doddapaneni, J. Hunt, H. Malinowski), CDR (Z. Zadeng)

# **NDA 21-525 (Photofrin for Injection)**

## **Attachment 1**

**Agency's letter dated 05/17/01**



DEPARTMENT OF HEALTH & HUMAN

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 20-451

Axcan Scandipharm Inc.  
c/o CanReg Inc.  
Attention: Anne M. Tomalin  
U.S. Regulatory Affairs  
450 North Lakeshore Drive  
Mundelein, Illinois 60060

Dear Ms. Tomalin:

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Photofrin (porfimer sodium) for Injection.

We have received your submissions dated May 29, October 30, and November 13, 1996, reporting on the following postmarketing study commitments.

1. Commitment 4  
Incorporate a standard in the routine HPLC assay, investigate the two wavelengths in the HPLC assay for detection of possible non-heme impurities, and validate a test for volatiles [ ]
2. Commitment 5  
Perform a validation study for the effectiveness of the [ ] process using Photofrin.
3. Commitment 3  
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 have reviewed your submissions and conclude that the above commitments were fulfilled.

The following commitments acknowledged in our December 27, 1995 letter are pending:

1. Commitment 1

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.

Status: The study report was submitted to NDA 20-451 on February 9, 2000 and is pending FDA review. Your May 4, 2001 communication states that you plan to update the labeling to incorporate this new information in May, 2001.

2. Commitment 2

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.

Status: Studies addressing pharmacokinetics of multiple dosing, and patients with hepatic impairment have not been completed. Study PHO-PK-001, designed to address gender effects, multiple dosing, and patients with hepatic impairment, was truncated due to photosensitivity reactions as noted in the May 18, 2000 submission. This submission also states that non-safety modifications (such as pharmacokinetic information) to the package insert will be submitted in due course as a separate supplement. Your May 4, 2001 communication states that you plan to update the labeling to incorporate this gender effects information in May, 2001. We also refer to your May 14, 2001 submission requesting release from the commitments concerning hepatic impairment and multiple dosing. This submission is under review by FDA.

If you have any questions, call Paul Zimmerman, Project Manager, at (301) 594-5775.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, M.D.

Director

Division of Oncology Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

# **NDA 21-525 (Photofrin for Injection)**

## **Attachment 2**

**Agency's letter dated 12/11/01**

**FOOD AND DRUG ADMINISTRATION  
OFFICE OF DRUG EVALUATION I**



**DIVISION OF ONCOLOGY DRUG PRODUCTS**

**HFD-150, 5600 Fishers Lane  
Rockville, Maryland 20857**

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**PHONE: (301) 594-5775      FAX: (301) 827-4590**

**TO: Kathryn Dunn/CanReg  
(847) 837-8825**

**FROM: Paul Zimmerman, Project Manager**

**Total number of pages, including cover sheet   1**

**Date: December 11, 2001**

**COMMENTS:      The following concern NDA 20-451 for Photofrin submission dated May 14,**

2001.

Exemption can not be granted based on the following considerations

- The current package insert indicates that patients may receive a second course of PDT 30 days after the initial therapy; up to three courses of PDT (each separated by a minimum of 30 days) can be given. This is different from what was described in the request letter, where it was stated that standard repeat doses are given at a minimum 90 days apart.
- Due to the long half-life of the drug, increased exposure in hepatic impairment patients remains a concern. A dose modification may be necessary for hepatic impaired patients which should be evaluated in a clinical study.

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Tien-Mien Chen  
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BIOPHARMACEUTICS

Suresh Doddapaneni  
8/16/02 07:30:40 AM  
BIOPHARMACEUTICS