

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022555Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

PATENT CERTIFICATION

Photocure certifies that all patents submitted to this New Drug Application are either owned solely by Photocure or are under an exclusive patent license agreement between Photocure and the patent owner (i.e., US 7,348,361).



Kjetil Hestdal, MD, PhD

President and CEO

Photocure ASA

20 May 2009

EXCLUSIVITY SUMMARY

NDA # 22555

SUPPL #

HFD # 160

Trade Name Cysview

Generic Name Hexaminolevulinate Hydrochloride

Applicant Name Photocure ASA

Approval Date, If Known May 28, 2010

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

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?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 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# 20965 Levulan (aminolevulinic acid hydrochloride)

NDA# 21415 Metvixia (methylaminolevulinate hydrochloride)

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. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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? If not applicable, answer NO.

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:

Study 305, titled, "A randomized, comparative, controlled phase 3, multicenter study of hexvix fluorescence cystoscopy and white light cystoscopy in the detection of papillary bladder cancer and the early recurrence rate in patients with bladder cancer."

note...multiple additional "supportive" studies were conducted by the applicant to support the approval however, these supportive studies were regarded as exploratory in nature while Study 305 was the definitive safety and efficacy study.

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"):

Study 305, titled, "A randomized, comparative, controlled phase 3, multicenter study of hexvix fluorescence cystoscopy and white light cystoscopy in the detection of papillary bladder cancer and the early recurrence rate in patients with bladder cancer." We refer to this as investigation 1;

note...multiple additional "supportive" studies were conducted by the applicant to support the approval however, these supportive studies were regarded as exploratory in nature while Study 305 was the definitive safety and efficacy study. We refer to these studies collectively as investigation 2.

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 # 51224 YES ! NO
 ! Explain:

Investigation #2
 IND # 51224 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 ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! 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:

=====

Name of person completing form: Scheldon Kress (MO), Alex Gorovets (MO), Ravi Kasliwal (Chemist), Thuy Nguyen (PM)
Title: See above
Date: May 28, 2010 (original) and June 2, 2010 (revised)

Name of Office/Division Director signing form: (Division of Medical Imaging Products/
Rafel Dwaine Rieves, M.D.
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

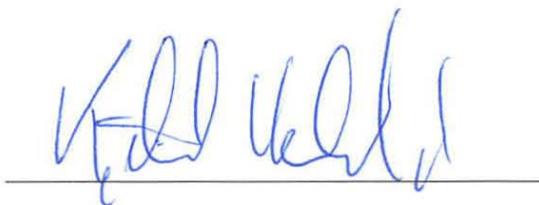
/s/

THUY M NGUYEN
06/02/2010

RAFEL D RIEVES
06/03/2010

DEBARMENT CERTIFICATION

I, the undersigned, hereby certify that Photocure ASA did not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this NDA application.



Kjetil Hestdal, PD, PhD
President & CEO
Photocure ASA

28 May 2009

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Christian Fekete	TITLE Chief Financial Officer
FIRM / ORGANIZATION Photocue ASA	
SIGNATURE 	DATE 2/8/09

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning (b) (6), who participated
Name of clinical investigator
as a clinical investigator in the submitted study PC B201/00 and PC B301/01
Name of
clinical study, is submitted in accordance with 21 CFR part 54. The
named individual has participated in financial arrangements or holds financial interests that are
required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Christian Fekete	TITLE Chief Financial Officer
FIRM / ORGANIZATION Photocure ASA	
SIGNATURE 	DATE 2/5/09

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning (b) (6), who participated
Name of clinical investigator

A randomized comparative phase III, 2-centre study of Hexvix®
fluorescence cystoscopy and standard cystoscopy in patients with
as a clinical investigator in the submitted study superficial bladder cancer.
Name of

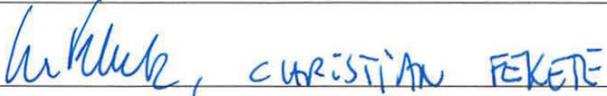
clinical study, is submitted in accordance with 21 CFR part 54. The

named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Christian Fekete	TITLE Chief Financial Officer
FIRM / ORGANIZATION Photocure ASA	
SIGNATURE 	DATE 5/19/09

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857



Food and Drug Administration
10903 New Hampshire Avenue
Document Control Room W-O66-0609
Silver Spring, MD 20993-0002

Ms. Susie Chen
Director of Regulatory and Legal Affairs
Karl Storz Endoscopy-America, Inc.
2151 E. Grand Avenue
EL SEGUNDO CA 90245

MAY 28 2010

Re: P050027
Karl Storz Photodynamic Diagnostic D-Light C (PDD) System
Filed: July 31, 2005
Amended: August 29 and November 3, 2005; February 2, July 18 and November 13,
2006; February 22, August 14 and November 19, 2007; March 31, and August 1, 2008;
January 21, February 19, March 5, April 30, May 8, September 8 and September 29 and
November 11, 2009
Procode: OAY

Dear Ms. Chen:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Karl Storz Photodynamic Diagnostic D-Light C (PDD) System. The Karl Storz Photodynamic Diagnostic D-Light C (PDD) System in combination with the optical imaging drug Cysview® (hexaminolevulinate hydrochloride) for Intravesical Solution is indicated for photodynamic blue light cystoscopy, as an adjunct to white light cystoscopy for the detection of non-muscle invasive papillary cancer of the bladder in patients suspected or known to have the lesion on the basis of a prior cystoscopy. We are pleased to inform you that the PMA for this combination product is approved in concurrence with CDER approval of the NDA for Cysview® (hexaminolevulinate hydrochloride) for Intravesical Solution.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). FDA has determined that this restriction on sale and distribution is necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The

Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the Annual Report requirements, we remind you of your postmarketing study commitments agreed to within your NDA submission and as described in your NDA Approval Order listed below:

1. A prospective, randomized, controlled clinical study that will assess the safety and efficacy of repetitive use of Cysview in the detection of bladder cancer.
2. A prospective, randomized, controlled clinical study that will assess the safety and efficacy of Cysview in the detection of carcinoma *in situ* of the bladder.

You may address both of these postmarketing study commitments by the completion of a single, well-designed clinical study that addresses the individual study expectations, as listed above.

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA.

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process"

(www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including *in vitro* diagnostic devices, are required to

report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or
2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at

www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Dockets Management Branch, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final

printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing. One of those three copies may be an electronic copy (eCopy), in an electronic format that FDA can process, review and archive (general information:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/Pre-marketSubmissions/ucm134508.htm>; clinical and statistical data:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/Pre-marketSubmissions/ucm136377.htm>)

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Mary J. Cornelius at 301-796-7001.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Christy Foreman" followed by "for".

Christy Foreman
Acting Office Director
Office of Device Evaluation
Center for Devices and Radiological Health

FDA – CDER DIVISION OF MEDICAL IMAGING PRODUCTS (DMIP)

INTERNAL TEAM MEETING MINUTES

NDA: 22555

DRUG NAME: Cysview

EDR SUBMISSION DATE: March 31, 2010

SPONSOR: Photocure ASA

MEETING DATE: Wednesday, May 26, 2010

PARTICIPANTS

Young-Moon Choi, Ph.D., PK Team Leader, Div of Medical Imaging Products (DMIP)
Mary Jo Cornelius, R.N., Reviewer, Center for Device and Radiological Health (CDRH)
Anne Crandall, Pharm.D., Reviewer, OSE-DMEPA
Alex Gorovets, M.D., Primary Clinical Team Leader, DMIP
Ravi Kasliwal, Ph.D., Chemistry Reviewer, DMIP
Scheldon Kress, M.D., Clinical Reviewer, DMIP
Angela Krueger, Regulatory Advisor, CDRH
Bayo Lanionu, P/T Reviewer and Team Leader, DMIP
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead, DMIP
Thuy Nguyen, M.P.H., Senior Regulatory Health Project Manager, DMIP
Rafel Dwaine Rieves, M.D., Division Director, DMIP
Michelle Safarik, Pharm.D., Reviewer, DDMAC
Lucie Yang, M.D., Ph.D., Clinical Reviewer, DMIP

AGENDA: Team Meeting - To discuss the CDRH review status and regulatory action regarding CDER NDA EDR resubmission dated March 31, 2010.

CDRH stated they do not have any revisions to CDER's *draft* drug "approval" letter of May 25, 2010.

CDRH has not forwarded the *draft* device PMA action letter to CDER as requested.

CDRH mentioned that the *draft* PMA has not been forwarded as of yet to Janine Morris who will sign off on the PMA action letter.

CDER would like to issue an "approval" regulatory action on Friday, May 28, 2010, to which CDRH stated they will make an effort to take an action on the PMA simultaneously on the same day.

Minutes Recorded By: T.Nguyen, DMIP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THUY M NGUYEN
05/26/2010

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22555: Cysview, submission dated March 31, 2010, FDA Labeling / Label Information Requests dated May 6 and 7, FDA Labeling / Label Response dated May 7, Sponsor Revised Labeling and Label submission dated May 17, FDA Labeling / Label and Post-Marketing Commitment Information Request dated May 19, and Sponsor Revised Labeling and Label submission dated May 20, the FDA has the following Label / Labeling Information Request – May 26, 2010.

By 9:00 am, US EST, Thursday, May 27, 2010, provide a response to my attention via email: Thuy.Nguyen@fda.hhs.gov, and follow-up with an official response by 3:00 pm, US EST, May 27, 2010, to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA LABEL INFORMATION REQUEST

1. Provide mock-up of the current revised carton, container and vial label / labeling that includes all the content, colors, and actual format.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
05/26/2010

FDA – CDER DIVISION OF MEDICAL IMAGING PRODUCTS (DMIP)

INTERNAL WRAP-UP MEETING MINUTES

NDA: 22555

DRUG NAME: Cysview

EDR SUBMISSION DATE: March 31, 2010

SPONSOR: Photocure ASA

MEETING DATE: Wednesday, May 19, 2010

PARTICIPANTS

Young-Moon Choi, Ph.D., Clin Pharm Team Leader, DMIP
Mary Jo Cornelius, RN, Reviewer, Center for Devices and Radiological Health (CDRH)
Alex Gorovet, M.D., Clinical Team Leader, DMIP
Ravi Kasliwal, Ph.D., Chemistry Reviewer, DMIP
Scheldon Kress, M.D., Primary Clinical Reviewer, DMIP
Patricia Love, M.D., M.B.A., Associate Director, Office of Combination Products
Thuy Nguyen, M.P.H., Regulatory Health Project Manager, DMIP
Dwayne Rieves, M.D., Division Director, DMIP
Michelle Safarik, Pharm.D., Reviewer, DDMAC
Lucie Yang, M.D., Ph.D., Clinical Reviewer, DMIP

AGENDA: NDA Wrap-Up Meeting - To discuss the review status and regulatory action of the NDA EDR resubmission dated March 31, 2010.

CDER: Clinical, CMC, P\T, PK, OSE-DMEPA, and DDMAC reviews are in DARRTS.

CDRH: Review has been received from Xin Fu, Ph.D. and CDRH stated they will be Able to issue a regulatory action on the PMA simultaneously with CDER action by May 28, 2010.

Labeling and Labels: Additional CDER labeling \ label comments and information request along with post-marketing commitments will be forwarded to the Sponsor.

Goal Date: May 28, 2010
PDUFA Due Date: June 1, 2010

Minutes Recorded By: T.Nguyen, DMIP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
05/24/2010

FDA – CDER DIVISION OF MEDICAL IMAGING PRODUCTS (DMIP)

INTERNAL FILING\TEAM\LABELING MEETING MINUTES

NDA: 22555

DRUG NAME: Cysview

EDR SUBMISSION DATE: March 31, 2010

SPONSOR: Photocure ASA

MEETING DATE: Thursday, April 22, 2010

PARTICIPANTS

Shaw T. Chen, M.D., Deputy Director, Office of Drug Evaluation IV
Mary Jo Cornelius, R.N., Reviewer, Center for Device and Radiological Health (CDRH)
Anne Crandall, Pharm.D., Safety Evaluator, OSE-DMEPA
Alex Gorovets, M.D., Clinical Team Leader, DMIP
Melina Griffis, Pharm.D., Team Leader, OSE-DMEPA
Carol Holquist, R.Ph., Director, OSE-DMEPA
Ravi Kasliwal, Ph.D., Chemistry Reviewer, DMIP
Scheldon Kress, M.D., Clinical Reviewer, DMIP
Bayo Lanionu, Ph.D., P\T Reviewer and Team Leader, DMIP
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead, DMIP
Patricia Love, M.D., M.B.A., Associate Director, Office of Combination Products
Thuy Nguyen, M.P.H., Senior Regulatory Health Project Manager, DMIP
Rafel Dwaine Rieves, M.D., Division Director, DMIP

AGENDA: NDA Filing, Team, and Labeling Meeting - To discuss the review status, timeline, and labeling\labels of the NDA EDR resubmission dated March 31, 2010.

CDER: The NDA is fileable under a Class 1 review with a PDUFA Due Date of June 1, 2010.

CDRH: Facility inspections have been completed and CDRH plans to issue an action on the PMA along with CDER action of the NDA.

Labeling and Labels: The Sponsor's proposed labeling and labels in the submission dated 03\31\10, were discussed. FDA labeling \ label comments will be forwarded to the Sponsor when appropriate.

Minutes Recorded By: T.Nguyen, DMIP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
05/20/2010

FDA – CDER DIVISION OF MEDICAL IMAGING PRODUCTS (DMIP)

INTERNAL TEAM AND LABELING MEETING MINUTES

NDA: 22555

DRUG NAME: Cysview

EDR SUBMISSION DATE: March 31, 2010

SPONSOR: Photocure ASA

MEETING DATE: Wednesday, April 28, 2010

PARTICIPANTS

Young-Moon Choi, Ph.D., PK Team Leader, Div of Medical Imaging Products (DMIP)
Anne Crandall, Pharm.D., Reviewer, OSE-DMEPA
Alex Gorovets, M.D., Primary Clinical Team Leader, DMIP
Melina Griffis, Pharm.D., Team Leader, OSE-DMEPA
Christy John, Ph.D., PK Reviewer, DMIP
Ravi Kasliwal, Ph.D., Chemistry Reviewer, DMIP
Scheldon Kress, M.D., Clinical Reviewer, DMIP
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead, DMIP
Thuy Nguyen, M.P.H., Senior Regulatory Health Project Manager, DMIP
Rafel Dwaine Rieves, M.D., Division Director, DMIP
Michelle Safarik, Pharm.D., Reviewer, DDMAC
Lucie Yang, M.D., Ph.D., Clinical Reviewer, DMIP

AGENDA: Team, and Labeling Meeting - To discuss the review status, timeline, and labeling\labels of the NDA EDR resubmission dated March 31, 2010.

CDER Review Status: Ongoing

CDER Facility Inspection: Pending

Time-Line: All reviews due into DARRTS by May 14, 2010.

Labeling and Labels: FDA labeling \ label comments will be forwarded to the Sponsor when appropriate.

CDRH Review Status: CDRH was not in attendance. CDER will ask CDRH for the current draft PMA labeling.

Minutes Recorded By: T.Nguyen, DMIP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
05/20/2010

FDA – CDER DIVISION OF MEDICAL IMAGING PRODUCTS (DMIP)

INTERNAL MIDCYCLE\TEAM\LABELING MEETING MINUTES

NDA: 22555
DRUG NAME: Cysview
EDR SUBMISSION DATE: March 31, 2010
SPONSOR: Photocure ASA
MEETING DATE: Thursday, May 6, 2010

PARTICIPANTS

Young-Moon Choi, Ph.D., PK Team Leader, Div of Medical Imaging Products (DMIP)
Alex Gorovets, M.D., Primary Clinical Team Leader, DMIP
Melina Griffis, Pharm.D., Team Leader, DMEPA, OSE-DMEPA
Christy John, Ph.D., PK Reviewer, DMIP
Ravi Kasliwal, Ph.D., Chemistry Reviewer, DMIP
Bayo Laniyonu, Ph.D., P/T Reviewer and Team Leader, DMIP
Patricia Love, M.D., M.B.A., Associate Director, Office of Combination Products
Lou Marzella, M.D., Acting Deputy Director\Clinical Team Leader, DMIP
Thuy Nguyen, M.P.H., Senior Regulatory Health Project Manager, DMIP
Rafel Dwaine Rieves, M.D., Division Director, DMIP
Michelle Safarik, Pharm.D., Reviewer, DDMAC
Lucie Yang, M.D., Ph.D., Non-primary Clinical Reviewer, DMIP

AGENDA: NDA Midcycle, Team, and Labeling Meeting - To discuss the review status, timeline, and labeling\labels of the NDA EDR resubmission dated March 31, 2010.

The Mid-Cycle presentation was presented by Alex Gorovets, M.D., CDER.

Time-Line: All reviews due into DARRTS by May 14, 2010.

CDER Facility Inspection: Pending

Labeling and Labels: FDA labeling \ label comments will be forwarded to the Sponsor when appropriate.

CDRH Review Status: CDRH was not in attendance. OCP suggested that a consult be forwarded to the CDRH branch regarding the catheter.

Minutes Recorded By: T.Nguyen, DMIP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
05/20/2010

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22555: Cysview, submission dated March 31, 2010, FDA Labeling \ Label Information Requests dated May 6 and 7, and Sponsor Revised Labeling and Label submission dated May 17, the FDA has the following Labeling \ Label and Post-Marketing Commitment Information Request – May 19, 2010. See attachments - MS Word Doc (in email) and PDF (within this document).

By 12:00 pm, US EST, Thursday, May 20, 2010, provide a response regarding the Post-Marketing Commitment and with regards to the labeling and labels, forward a response along with both a track-change and clean revised version of the revised draft labeling and labels in both MS Word Doc and PDF, to my attention via email: Thuy.Nguyen@fda.hhs.gov, and follow-up with an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA POST-MARKETING COMMITMENTS

Provide a statement that describes your agreement to perform the following Post-Marketing Commitments as well as a plan to address the following Post-Marketing Commitments (PMCs) outlined below:

1. Complete a prospective, randomized, controlled clinical study that will assess the safety and efficacy of repetitive use of Cysview in the detection of bladder cancer. The study's design will incorporate elements (such as sample size estimates and analytical plans) sufficient to provide robust evidence to support the major study objectives.

Protocol submission: month, year

Study start: month, year

Final report submission: month, year

FDA POST-MARKETING COMMITMENTS (cont.)

2. Complete a prospective, randomized, controlled clinical study that will assess the safety and efficacy of Cysview in the detection of carcinoma *in situ* of the bladder. The study's design will incorporate elements (such as sample size estimates and analytical plans) sufficient to provide robust evidence to support the major study objectives.

Protocol submission: month, year

Study start: month, year

Final report submission: month, year

You may modify the text to provide additional details and you may wish to combine the PMCs into a single study. Supply specific dates (e.g., May, 2011) for the time lines.

14 Pages Draft Labeling have been
Withheld in Full as B4 (CCI/TS)
Immediately Following this Page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

THUY M NGUYEN
05/19/2010



NDA 022555

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Photocure ASA
c/o Cato Research, Ltd.
Westpark Corporate Center
4364 South Alston Avenue
Durham, NC 27713

ATTENTION: Lynda Sutton, B.S.
Chief Regulatory Officer

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) resubmission dated March 31, 2010, received April 1, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hexaminolevulinate Hydrochloride Solution, 100 mg for bladder instillation.

We also refer to your February 10, 2010, correspondence, received February 12, 2010, requesting review of your proposed proprietary name, Cysview. We have completed our review of the proposed proprietary name, Cysview and have concluded that it is acceptable.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Catherine Carr, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2311. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Thuy Nguyen at (301) 796-2050.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

CAROL A HOLQUIST
05/10/2010

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH
Division: Gastroenterology and Renal Devices Branch (GRDB)
Mail Code: HF_- Z: 470
Consulting Reviewer Name: Carolyn Neuland, Microbiology Team Leader\Supervisor
Building/Room #: WO #66 - Room 226
Phone #: 301 -796-6523
Fax #:
Email Address: Carolyn.Neuland@fda.hhs.gov
RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER
Division: Division of Medical Imaging and Hematology Products
Mail Code: HFD-160
Requesting Reviewer Name: Scheldon Kress, MD (via PM)
Building/Room #: WO 22 - 2179
Phone#: 301-796-1391
Fax #:
Email Address: Scheldon.Kress@fda.hhs.gov
RPM/CSO Name and Mail Code: Thuy Nguyen
Requesting Reviewer's Concurring Supervisor's Name: Alex Gorovets, MD

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 05\07\10

Submission/Application Number: NDA 22555

Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product

Submission Receipt Date: 03\31\10

Name of Product: Cysview

Requested Completion Date: **May 17, 2010**

Submission Type: NDA

Official Submission Due Date: June 1, 2010

Name of Firm: Photocure

Intended Use: A drug-device combination product - Cysview Solution is a diagnostic imaging agent indicated for photodynamic blue light cystoscopy performed with Karl Storz Photodynamic Diagnosis (PDD) system, as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate): See email from Thuy Nguyen (PM) dated 05\07\10, for background information attachment w\FDA draft labeling to Sponsor (as of 05\06\10) and see EDR for CDER - NDA resubmission dated 03\31\10.

Questions to GRDB:

1. Is the assay sufficient to determine if there are any concerns for using the drug with these catheter materials?
2. Are there any limitations or cautions for the catheter that should be in the Cysview labeling?

Documents to be returned to Requesting Reviewer? π Yes π No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review π Collaborative Review

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
05/07/2010

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22555: Cysview, submission dated March 31, 2010, the FDA has the following Label Comments \ Information Request – May 7, 2010.

By 12:00 pm, US EST, Monday, May 17, 2010, forward a response along with both a track-change and clean revised version of the revised labels in both MS Word Doc and PDF, to my attention via email: Thuy.Nguyen@fda.hhs.gov, and follow-up with an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA LABEL COMMENTS AND INFORMATION REQUEST

Cysview container and carton label comments:

[REDACTED] (b) (4)

DILUENT vial label comments:

- Remove the box from the principal display panel [REDACTED] (b) (4)
- Relocate the [REDACTED] (b) (4) statement which is located in the upper area of the principal display panel so that it is more center. Furthermore, revise the statement so that it appears more prominent than “Cysview”.
- Decrease the prominence of the proprietary name, “Cysview”, on the principal display panel.
- Remove the established name and the route of administration from the principle display panel.

Carton label comments:

- Revise the statement on the principle display panel which describes storage of the solution after reconstitution [REDACTED] (b) (4)

[REDACTED]

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
05/07/2010

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22555: Cysview, submission dated March 31, 2010, FDA labeling information request of May 6, FDA label information request of May 7, and your email correspondence of May 7, the FDA has the following Labeling and Label Comments \ Response – May 7, 2010.

If you have not done so already, forward your email correspondence of May 7, 2010, to the FDA as a formal submission via Gateway \ GSR electronic submission as with all correspondences\submissions regarding NDA 22555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA Labeling and Label Comments \ Response

Regarding your email correspondence, May 7, 2010, to the FDA draft labeling and label comments of May 6 and 7, 2010, we have the following comments:

1. Sponsor Comments to the FDA Labeling Comment in 2.2: FDA finds it acceptable.
2. Sponsor Comments to the FDA Labeling Comment 2.3: FDA finds it acceptable, but will have to see the actual figures.
3. Sponsor Comments to the FDA Labeling Comment 2.5: FDA has noted your comments.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
05/07/2010

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22555: Cysview, submission dated March 31, 2010, the FDA has the following Labeling Information Request – May 6, 2010. See attachments - MS Word Doc (in email) and PDF (within this document).

By 12:00 pm, US EST, Monday, May 17, 2010, forward a response along with both a track-change and clean revised version of the revised draft labeling in both MS Word Doc and PDF, to my attention via email: Thuy.Nguyen@fda.hhs.gov, and follow-up with an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

11 Pages Draft Labeling have been Withheld
in Full as B4 (CCI/TS) Immediately Following
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
05/06/2010



NDA 22555

ACKNOWLEDGE CLASS 1 COMPLETE RESPONSE

Cato Research, Ltd (for Photocure ASA)
Attn: Lynda Sutton, Chief Regulatory Officer
4364 S. Alston Ave.
Durham, NC 27713-2220

Dear Ms. Sutton (for Photocure ASA):

We acknowledge receipt on April 1, 2010, of your resubmission dated March 31, 2010, to your New Drug Application for Hexaminolevulinate Hydrochloride Kit.

We consider this a complete, Class 1 Response to our action letter of December 30, 2009. Therefore, the User Fee Goal Date is June 1, 2010.

If you have any questions, please contact Ms. Thuy Nguyen, M.P.H., Senior Regulatory Health Project Manager at (301) 796-2050 or Thuy.Nguyen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thuy Nguyen, M.P.H.
Senior Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
04/26/2010



NDA 22555

FILING COMMUNICATION

Cato Research, Ltd. (for Photocure ASA)
Attn: Lynda Sutton, Chief Regulatory Officer
4364 S. Alston Ave.
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your new drug application (NDA) dated March 31, 2010, received April 1, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Hexaminolevulinate Hydrochloride Kit.

We also refer to your submission dated April 9, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is Priority. Therefore, the User Fee Goal Date is June 1, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 7, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

NDA 22555: Hexaminolevulinate Hydrochloride Kit

Page 2

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, contact Ms. Thuy M. Nguyen, M.P.H., Senior Regulatory Health Project Manager, at (301) 796-2050 or Thuy.Nguyen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D., Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
04/26/2010

RAFEL D RIEVES
04/26/2010

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH
Division: DRARD

Mail Code: HF_- Z: 470
Consulting Reviewer Name: Mary Jo Cornelius, RN
Building/Room #: 66 - 0204
Phone #: 301 -796-7001
Fax #:
Email Address: Mary.Cornelius@fda.hhs.gov
RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER
Division: Division of Medical Imaging and Hematology Products
Mail Code: HFD-160
Requesting Reviewer Name: Scheldon Kress, MD
Building/Room #: WO 22 - 2179
Phone#: 301-796-1391
Fax #:
Email Address: Scheldon.Kress@fda.hhs.gov
RPM/CSO Name and Mail Code: Thuy Nguyen
Requesting Reviewer's Concurring Supervisor's Name: Alex Gorovets, MD

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 04\20\10
Submission/Application Number: NDA 22555
Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product
Submission Receipt Date: 03\31\10
Name of Product: Cysview

Requested Completion Date: **April 30, 2010**
Submission Type: NDA
Official Submission Due Date: June 1, 2010
Name of Firm: Photocure

Intended Use: A drug-device combination product - Cysview Solution is a diagnostic imaging agent indicated for photodynamic blue light cystoscopy performed with Karl Storz Photodynamic Diagnosis (PDD) system, as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate): See email from Thuy Nguyen dated 04\02\10, for the EDR link to CDER - NDA resubmission dated 03\31\10. Please review the NDA resubmission along with the Sponsor's proposed DRAFT labeling and labels and provide feedback by 04\20\10 in prep for CDER Filing Meeting (04\22\10), and final consult review by April 30, 2010. Referenced PMA 050027

Documents to be returned to Requesting Reviewer? π Yes π No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review π Collaborative Review

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
04/20/2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/s/

THUY M NGUYEN
04/19/2010

***CONFIDENTIAL**

FDA - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY DRUG PRODUCTS (DMIHP)

TYPE B INDUSTRY MEETING MINUTES

NDA: 22555

DRUG NAME: Hexaminolevulinate Hydrochloride Kit

SPONSOR: Photocure ASA

DATE: Wednesday, March 3, 2010, at 1:30 pm

LOCATION: WO #22 – Conf Room 1417

SPONSOR PARTICIPANTS

Susie Chen, Director, Legal and Regulatory Affairs, Karl-Storz Endoscopy America

Desiree Germain, B.S., Assistant Project Manager, Cato Research

(b) (4)

Ingunn Munch Lindvig, PhD., Director of Regulatory Affairs

Fred Longenecker, Director, Regulatory Development, GE Healthcare

(b) (4)

Gry Stensrud, Ph.D., Pharmaceutical Director

Lynda Sutton, B.S., US Regulatory Agent for Photocure, Cato Research

Yngvil Kloster Thomas, M.Sc., Project Director

Elaine Wright, Global Director of Urology, GE Healthcare

Inger Ferner Heglund, Ph.D., Head of R&D, Photocure (via teleconference)

FDA PARTICIPANTS

Catherine Carr, Pharm.D., Project Manager, OSE, Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE)

Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader, Div of Medical Imaging and Hematology Products (DMIHP)

Shaw T. Chen, M.D., Deputy Director, Office of Non-Prescription Drugs (ONP)

Leah Christl, Ph.D., Associate Director, ONP

Mary Jo Cornelius, R.N., Reviewer, Center for Device and Radiological Health (CDRH)

Anne Crandall, Pharm.D., Safety Evaluator, OSE

Charles Ganley, M.D., Office Director, ONP

Alex Gorovets, M.D., Clinical Team Leader, DMIHP

NDA 22555: Hexaminolevulinate Hydrochloride Kit
Page 2

FDA PARTICIPANTS (cont.)

Melina Griffis, Pharm.D., Team Leader, DMEPA, OSE
Carol Holquist, R.Ph., Director, DMEPA, OSE
Joseph Kaminski, M.D., Clinical Reviewer, DMIHP
Ira Krefting, M.D., Safety Team Leader, DMIHP
Scheldon Kress, M.D., Primary Clinical Reviewer, DMIHP
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead, DMIHP
Patricia Love, M.D., M.B.A., Associate Director, Office of Combination Products
Susan Montenegro, Student Pharmacist, DMEPA, OSE
Lubna Najam, Pharm.D., Safety Evaluator, DMEPA, OSE
Thuy Nguyen, M.P.H., Senior Regulatory Health Project Manager, DMIHP
Yanli Ouyang, Ph.D., Pharm\Tox Reviewer, DMIHP
Rafel Dwaine Rieves, M.D., Division Director, DMIHP

AGENDA: To discuss the FDA Complete Response Letter of December 30, 2009, with regards to the original NDA submission dated June 30, 2009, and the FDA preliminary meeting response dated February 26, 2010 (see Attachment #1) to the Sponsor Meeting Package dated February 2, 2010.

Following the Sponsor's presentation (see EDR submission dated 03\08\10), the following were discussed:

Two Pre-Marketing Application (PMA) inspections were conducted in January and February 2010, and Center for Device and Radiological Health (CDRH) indicated that a regulatory action will be issued once the inspection reports are finalized. If there are no outstanding issues with the PMA, CDRH anticipates issuing an approvable letter since the approval of the PMA is linked to the simultaneous approval of the NDA.

The Sponsor will request in the NDA resubmission cover letter a 60-day review of the resubmission. The Sponsor plans to address the FDA Complete Response Letter dated 12\30\09, along with any issues from today's meeting, and provide an NDA resubmission by the end of March 2010.

The proprietary drug name review is currently underway with the FDA Office of Safety and Epidemiology (OSE). FDA clarified that while they understood that the Sponsor prefers to have an approved proprietary name by the time of the NDA approval, the NDA can be approved on the product established name and as such, the proprietary name review will not delay the approval of the NDA.

Meeting Question\Response #3 Discussion: The Sponsor explained that the vinyl catheter is the most practical for the usage\indication and are readily available on site. However, the FDA suggested that the labeling should state other alternative bladder catheters that could be used in an event that a vinyl catheter is unavailable. The labeling should state why other catheters would not be clinically appropriate or feasible.

Meeting Question\Response #3 Discussion (cont.):

Regarding the proposed figure/illustration, the shading of the funnel end of the catheter will be modified to address the FDA meeting comment\response. In other matters, the FDA stated data\information needs to be provided regarding the required retention time of the drug solution in the bladder and reflected in the labeling.

Meeting Question\Response #5a Discussion: The Sponsor will address in the labeling the causes of the false positives and the Sponsor stated that the labeling and training manual will be consistent.

Meeting Question\Response #5b Discussion: Regarding pivotal study PC B305\04, the Sponsor described a skin and subcutaneous adverse events (AEs) reported in patients who have received Hexaminolevulinate Hydrochloride (HH) and among patients in the white light only group who did not received HH. Within the resubmission, the Sponsor will discuss the potential for perineal skin irritation and\or sensitization. The Sponsor will also provide the instructions for post-void washing in the labeling and training manual.

Before the discussion of Meeting Question\Response #1, the Sponsor provided a demonstration of the reconstitution and preparation process which showed that the needle tip is removed and the syringe is capped only once.

Meeting Question\Response #1 Discussion: The Sponsor will update the new reconstitution and preparation process in the NDA resubmission, labeling and training manual. A discussed, a detachable syringe label or pictorial diagram will also be included as well the revised text and pictorial figures. Also, the Sponsor agreed to provide in the resubmission the data from the adaptor compatibility testing. The Sponsor will sufficiently describe in the labeling and training manual the reconstitution and preparation process as discussed and seen in the Sponsor's demonstration.

The FDA reiterated that the Sponsor should provide as much detailed information in the NDA resubmission, draft labeling and training manual as possible to minimize the FDA requests for additional detail, data, or missing information.

Note: Meeting Questions\Responses #2 and 4, were not discussed since the Sponsor did not need any further clarification.

ACTION ITEMS

1. The Sponsor will address the issues\comments discussed in the NDA resubmission, draft labeling and training manual and plans to submit the NDA resubmission by the end of March 2010.
2. The Sponsor will provide their slide presentation to the NDA as a formal submission and the FDA meeting minutes will be forwarded to the Sponsor.

Meeting Minutes Recorded By: T.Nguyen, DMIHP

ATTACHMENT #1

***CONFIDENTIAL**

FOOD AND DRUG ADMINISTRATION (FDA)

NDA 22555: "Hexvix"

Sponsor: Photocure ASA

TYPE B: INDUSTRY MEETING – March 3, 2010

Regarding the Meeting Package dated February 2, 2010, below are the FDA preliminary meeting responses\comments in preparation for the meeting, March 3, 2010, and may not be fully vetted internally and should not be considered as an official position of the FDA. It is shared with the Sponsor solely to promote a collaborative and successful discussion during the meeting. The FDA meeting minutes will reflect agreements and discussion and might not be consistent with these preliminary meeting responses\comments.

SPONSOR MEETING QUESTION #1

Does the Agency agree that the redeveloped reconstitution and preparation process described (FDA issue no. 2) is appropriate for submission in Photocure's Complete Response for preparation of Hexaminolevulinate Hydrochloride solution, as supported by the described documentation?

Photocure is in close collaboration with Karl Storz, the manufacturer of the Karl Storz D-Light C PDD system, to ensure the most timely approval possible of the Karl Storz D-Light C PDD system. The remaining outstanding item is the inspection of a Karl Storz facility in Tuttlingen, Germany, which is scheduled to occur 1-4 March 2010.

FDA RESPONSE #1

We agree that the new process of reconstitution and preparation as described in the Meeting Package dated February 2, 2010, is improved, however the recommendation in step 2 of the preparation directions [REDACTED] ^{(b) (4)} could introduce unintentional needle puncture/sharp injury and may also result in product spillage. We recommend that the needle tip be removed and the syringe capped only once during the preparation process. This should take place after the entire 50 mL of reconstituted solution is in the syringe and ready for administration. The package insert should be updated to reflect these instructions with an emphasis on the importance of capping the syringe to ensure that the needle is off the syringe to prevent inadvertent intravenous administration.

SPONSOR MEETING QUESTION #2

Does the Agency agree that the amended product administration procedures (FDA issue no. 4) are appropriate and sufficiently described for submission in Photocure's Complete Response?

FDA RESPONSE #2

We agree.

SPONSOR MEETING QUESTION #3

Does the Agency agree that the proposed Package Insert describes the cystoscopic examination procedure, the use of the product and its essential aspects (FDA issue no. 5) appropriate for submission in Photocure's Complete Response and that the contents and format of the proposed Training Manual are appropriate for submission in Photocure's Complete Response?

FDA RESPONSE #3

We remain concerned about the safety and reliability of the connection between the syringe and a urinary catheter.

Whereas the labeling states to avoid contact with the skin, we remain concerned that an appropriate bladder catheter be utilized to provide a rigorous connection between the Luer-lock syringe and catheter to ensure the absence of leakage before, during and after administration of the syringe contents into the bladder. Whereas the size of funnel ends of catheters varies, we recommend that you remedy this problem. The supplied information does not resolve our concern.

While it might be true that Luer-lock adapters are readily available in most hospitals, they may not be immediately available to the personnel about to administer your product into a "funnel ended" catheter. In such situations, we anticipate that the personnel utilizing sterile techniques may attempt to administer your product directly into the "funnel end" rather than seek out a Luer-adapter and bring it to the site.

Therefore, we suggest that you consider either specifically recommending use of a urinary catheter that provides a Luer-lock compatible connector for instillation or including a Luer-lock adapter in each of your product kits. This will ensure proper administration when "funnel ended" catheters are encountered by personnel attempting to instill your product into the bladder while maintaining sterility and safety for patient and health care provider.

NDA 22555: Hexaminolevulinate Hydrochloride Kit
Page 6

In reference to your diagram reproduced below, we recommend the use of additional shading in this diagram to more easily distinguish the Luer-adapter from the “funnel-end of the catheter.”



In addition, bladder catheter materials include silicone, latex, coatings, colorants and radio-opaque components. Coatings may consist of hydrogels, silver and antimicrobials. Hydrogel coatings contain different polymer materials from different manufacturers. Please comment on the issue of compatibility in relation to silicone and latex catheters with and without hydrogel coatings and possibly propose testing for such compatibility.

The NDA resubmission should include data demonstrating compatibility of the specific types of bladder catheters that may be used to administer Hexvix. The supplied information should identify the brands that have been tested for compatibility and others types (of marketed) catheters that have not been tested. Catheters impregnated with silver or antibiotics should be avoided.

Clarify whether physicians will have the option of leaving the bladder catheter in place during the one hour retention period for those patients who do not feel they will be able to retain the solution for the full hour. Which types of catheters could be recommended for this situation?

SPONSOR MEETING QUESTION #4

Does the Agency agree that the target population as described (FDA issue no. 6) is appropriate for submission in Photocure's Complete Response?

FDA RESPONSE #4.

We agree.

SPONSOR MEETING QUESTION #5

Does the Agency agree that the proposed revised Package Insert appropriately addresses the issues detailed in the Agency's Complete Response letter for submission in Photocure's Complete Response?

FDA RESPONSE #5

We will review the proposed package insert as part of the NDA resubmission review.

Some of the additional issues are stated below:

- A. We have not been able to locate reference within the label to the most common causes of false positive image fluorescence during Trademark photodynamic blue light cystoscopy.



We recommend that both the label and the Physician Training Manual are consistent, i.e., both provide similar information regarding the most common causes of false positive image fluorescence during Trademark photodynamic blue light cystoscopy.

- B. During the process of voluntary voiding after retaining your product for approximately an hour, some of your product (especially in the case of females) might remain on the perineal surface areas. You also recommend that "...care should be taken to avoid skin contact with Trademark Solution. However, if skin does come in contact with Trademark Solution, wash immediately with soap and water and dry off."

What has been your world-wide experience with the perineal spillage of your product causing sensitization and/or local dermatitis? You may wish to summarize this information at the upcoming meeting; more importantly, please supply the information within your resubmission. If perineal skin contact is to be expected, especially in females after post-retention voluntary voiding, consider recommending post-void wash routinely.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22555	----- GI-1	----- PHOTOCURE ASA	----- HEXVIX

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THUY M NGUYEN
03/30/2010

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

February 26, 2010

**Dear Ms. Lynda Sutton – Chief Regulatory Officer,
Cato Research (for Photocure ASA)
Office: (919) 361-2286
Email: lsutton@cato.com**

Regarding NDA 22555: “Hexvix”, please find attached the FDA Preliminary Meeting Response, February 26, 2010, to the Meeting Package dated February 2, 2010.

Please review and let me know (via email) by 9:00 am, EST, Tuesday, March 2, 2010, which specific Meeting Questions \ Responses Photocure ASA would like to discuss at the meeting on March 3, 2010.

If you have any questions, please feel free to contact me.

**Sincerely,
Thuy Nguyen
Senior Regulatory Health Project Manager
FDA CDER – Division of Medical Imaging and Hematology Products
(301) 796-2050**

*CONFIDENTIAL

FOOD AND DRUG ADMINISTRATION (FDA)

NDA 22555: "Hexvix"

Sponsor: Photocure ASA

TYPE B: INDUSTRY MEETING – March 3, 2010

Regarding the Meeting Package dated February 2, 2010, below are the FDA preliminary meeting responses\comments in preparation for the meeting, March 3, 2010, and may not be fully vetted internally and should not be considered as an official position of the FDA. It is shared with the Sponsor solely to promote a collaborative and successful discussion during the meeting. The FDA meeting minutes will reflect agreements and discussion and might not be consistent with these preliminary meeting responses\comments.

SPONSOR MEETING QUESTION #1

Does the Agency agree that the redeveloped reconstitution and preparation process described (FDA issue no. 2) is appropriate for submission in Photocure's Complete Response for preparation of Hexaminolevulinate Hydrochloride solution, as supported by the described documentation?

Photocure is in close collaboration with Karl Storz, the manufacturer of the Karl Storz D-Light C PDD system, to ensure the most timely approval possible of the Karl Storz D-Light C PDD system. The remaining outstanding item is the inspection of a Karl Storz facility in Tuttlingen, Germany, which is scheduled to occur 1-4 March 2010.

FDA RESPONSE #1

We agree that the new process of reconstitution and preparation as described in the Meeting Package dated February 2, 2010, is improved, however the recommendation in step 2 of the preparation directions [REDACTED] ^{(b) (4)} could introduce unintentional needle puncture/sharp injury and may also result in product spillage. We recommend that the needle tip be removed and the syringe capped only once during the preparation process. This should take place after the entire 50 mL of reconstituted solution is in the syringe and ready for administration. The package insert should be updated to reflect these instructions with an emphasis on the importance of capping the syringe to ensure that the needle is off the syringe to prevent inadvertent intravenous administration.

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SPONSOR MEETING QUESTION #3

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FDA RESPONSE #3

We remain concerned about the safety and reliability of the connection between the syringe and a urinary catheter.

Whereas the labeling states to avoid contact with the skin, we remain concerned that an appropriate bladder catheter be utilized to provide a rigorous connection between the Luer-lock syringe and catheter to ensure the absence of leakage before, during and after administration of the syringe contents into the bladder. Whereas the size of funnel ends of catheters varies, we recommend that you remedy this problem. The supplied information does not resolve our concern.

While it might be true that Luer-lock adapters are readily available in most hospitals, they may not be immediately available to the personnel about to administer your product into a “funnel ended” catheter. In such situations, we anticipate that the personnel utilizing sterile techniques may attempt to administer your product directly into the “funnel end” rather than seek out a Luer-adapter and bring it to the site.

Therefore, we suggest that you consider either specifically recommending use of a urinary catheter that provides a Luer-lock compatible connector for instillation or including a Luer-lock adapter in each of your product kits. This will ensure proper administration when “funnel ended” catheters are encountered by personnel attempting to instill your product into the bladder while maintaining sterility and safety for patient and health care provider.

In reference to your diagram reproduced below, we recommend the use of additional shading in this diagram to more easily distinguish the Luer-adapter from the “funnel-end of the catheter.”



In addition, bladder catheter materials include silicone, latex, coatings, colorants and radio-opaque components. Coatings may consist of hydrogels, silver and antimicrobials. Hydrogel coatings contain different polymer materials from different manufacturers. Please comment on the issue of compatibility in relation to silicone and latex catheters with and without hydrogel coatings and possibly propose testing for such compatibility.

The NDA resubmission should include data demonstrating compatibility of the specific types of bladder catheters that may be used to administer Hexvix. The supplied information should identify the brands that have been tested for compatibility and others types (of marketed) catheters that have not been tested. Catheters impregnated with silver or antibiotics should be avoided.

Clarify whether physicians will have the option of leaving the bladder catheter in place during the one hour retention period for those patients who do not feel they will be able to retain the solution for the full hour. Which types of catheters could be recommended for this situation?

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We agree.

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Does the Agency agree that the proposed revised Package Insert appropriately addresses the issues detailed in the Agency's Complete Response letter for submission in Photocure's Complete Response?

FDA RESPONSE #5

We will review the proposed package insert as part of the NDA resubmission review.

Some of the additional issues are stated below:

- A. We have not been able to locate reference within the label to the most common causes of false positive image fluorescence during Trademark photodynamic blue light cystoscopy.



We recommend that both the label and the Physician Training Manual are consistent, i.e., both provide similar information regarding the most common causes of false positive image fluorescence during Trademark photodynamic blue light cystoscopy.

- B. During the process of voluntary voiding after retaining your product for approximately an hour, some of your product (especially in the case of females) might remain on the perineal surface areas. You also recommend that "...care should be taken to avoid skin contact with Trademark Solution. However, if skin does come in contact with Trademark Solution, wash immediately with soap and water and dry off."

What has been your world-wide experience with the perineal spillage of your product causing sensitization and/or local dermatitis? You may wish to summarize this information at the upcoming meeting; more importantly, please supply the information within your resubmission. If perineal skin contact is to be expected, especially in females after post-retention voluntary voiding, consider recommending post-void wash routinely.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22555	----- GI-1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

THUY M NGUYEN
02/26/2010



NDA 22-555

MEETING GRANTED

Cato Research, Ltd (for Photocure ASA)
Attn: Lynda Sutton, Chief Regulatory Officer
4364 S. Alston Ave.
Durham, NC 27713-2220

Dear Ms. Sutton (for Photocure ASA):

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Hexvix".

We also refer to the correspondence dated January 11, 2010, requesting a meeting to discuss the FDA Complete Response Letter dated December 30, 2009. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type B meeting.

The meeting is scheduled as follow:

Date: Wednesday, March 3, 2010
Time: 1:30 – 3:00 pm, EST
Location: Food and Drug Administration
10903 New Hampshire Ave
White Oak Building #22, Conference Room #1417
Silver Spring, MD 20993
FDA Contact: Thuy Nguyen, M.P.H., Senior Regulatory Health Project Manager
(301) 796-2050
Dial-In #: Provide a toll-free number (with 15 lines) in the Meeting Package.

FDA Participants (tentative):

Catherine Carr, Pharm.D., Project Manager, Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE)
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader, Div of Medical Imaging and Hematology Products (DMIHP)
Mary Jo Cornelius, R.N., Reviewer, Center for Device and Radiological Health (CDRH)
Anne Crandall, Pharm.D., Safety Evaluator, OSE
Alex Gorovets, M.D., Clinical Team Leader, DMIHP
Melina Griffis, Pharm.D., Team Leader, DMEPA, OSE
Christy John, Ph.D., Clinical Pharmacology Reviewer, DMIHP
Ravi Kasliwal, Ph.D., Chemistry Reviewer, DMIHP
Scheldon Kress, M.D., Clinical Primary Reviewer, DMIHP
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead, DMIHP

FDA PARTICIPANTS (cont.)

Patricia Love, M.D., Deputy Director, Office of Combination Products
Janine Morris, Ph.D., Team Leader, CDRH
Anthony Mucci, Ph.D., Statistical Reviewer, DMIHP
Thuy Nguyen, M.P.H., Senior Regulatory Health Project Manager, DMIHP
Yanli, Ouyang, Ph.D., Pharm\Tox Reviewer, DMIHP
Rafel Dwaine Rieves, M.D., Division Director, DMIHP
Denise Toyer, Pharm.D., Deputy Director, DMEPA, OSE
Jyoti Zalkikar, Ph.D., Statistical Team Leader, DMIHP

Arrive 30 minutes before the meeting with a valid government-issued photo ID for security clearance.

For participants who are not US citizens, complete the attached Foreign Visitor Data Request Form (for each participant) and forward to the forms to me by February 3, 2010 (via email).

Provide (6) desk hard copies in addition to the Gateway electronic submission of the Meeting Information Package by February 3, 2010, one month prior to the meeting to the following addresse below:

Thuy Nguyen, M.P.H., Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Ave
White Oak Building #22, Room #2315
Silver Spring, MD 20993

If the materials presented in the Meeting Information Package are inadequate to justify holding a meeting, or if we do not receive the Meeting Package by February 3, 2010, we may cancel or reschedule the meeting.

If you have any questions, please feel free to contact me at (301) 796-2050 or Thuy.Nguyen@fda.hhs.gov.

Sincerely,
{See appended electronic signature page}
Thuy Nguyen, M.P.H.
Senior Regulatory Health Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Enclosure: Foreign Visitor Data Request Form

CONFIDENTIAL**FOREIGN VISITOR DATA REQUEST FORM**

VISITOR'S FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER: COUNTRY THAT ISSUED PASSPORT: ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	March 3, 2010 – 1:30 pm
MEETING ENDING DATE AND TIME	March 3, 2010 – 3:00 pm
PURPOSE OF MEETING	FDA Type B Meeting
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	US Food and Drug Administration 10903 New Hampshire Ave White Oak Building #22, Conference Room #1417 Silver Spring, MD 20993
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Thuy Nguyen, Regulatory Health Project Manager Food and Drug Administration 10903 New Hampshire Ave White Oak Building #22, Room #2315 Silver Spring, MD 20993 (301) 796-2050
ESCORT INFORMATION (If different from Hosting Official)	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	GI-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
01/14/2010

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 11, 2010
TIME: 1:00 – 1:30 PM EST
LOCATION: Teleconference, WO Bldg 22, Room 4157
APPLICATION: NDA 022555
DRUG NAME: Hexaminolevulinate hydrochloride kit
TYPE OF MEETING: Guidance Meeting

MEETING CHAIR: Ann Crandall, Safety Evaluator, DMEPA, OSE

MEETING RECORDER: Catherine Carr, Safety Regulatory Project Manager, OSE

FDA ATTENDEES: (Title and Office/Division)

Office of Surveillance and Epidemiology

Kellie Taylor, Pharm.D. M.P.H., Associate Director, DMEPA, OSE
Melina Griffis, R.Ph., Team Leader, DMEPA, OSE
Anne Crandall, Pharm.D., Safety Evaluator, DMEPA, OSE
Catherine Carr, M.Sc., Safety Regulatory Project Manager, OSE

Division of Medical Imaging and Hematology

Alex Gorovets, M.D., Clinical Team Leader, DMIHP, OND
Scheldon Kress, M.D., Medical Officer, DMIHP, OND
Lucie Yang, M.D., Ph.D., Medical Officer, DMIHP, OND
Thuy Nguyen, M.P.H., Regulatory Health Project Manager, DMIHP, OND

EXTERNAL CONSTITUENT ATTENDEES:

Photocure ASA/Cato Research

Yngvil Thomas, M.Sc., Project Director, Photocure ASA
Ingunn Munch Lindvig, Ph.D., Director Regulatory Affairs, Photocure ASA
Inger Ferner Heglund, Vice President R&D, Photocure ASA
Fred Longenecker, Director, Regulatory Development, GE Healthcare
Susan Elliott, Senior Manager, Regulatory Labeling and Compliance, GE Healthcare
Will Lee, Director of Regulatory Affairs, Cato Research

BACKGROUND:

Reference is made to [REDACTED] (b) (4) for the tradename review for hexaminolevulinate hydrochloride.

The sponsor submitted a request for proprietary name review for hexaminolevulinate hydrochloride, an imaging agent, which was subject to a pending NDA application (PDUFA date

December 30, 2009). Upon review of the August 25, 2009 submission, DMEPA concluded that the name Hexvix was unacceptable and issued a denial letter, dated November 9, 2009.

On November 20, 2009, the sponsor submitted a request for reconsideration of the name Hexvix, but subsequently withdrew the submission on December 18, 2009, after proposing four additional proprietary names on December 16, 2009. This submission provided for the proposed proprietary names, [REDACTED] (b) (4), in order of preference. Upon preliminary review of this submission, DMEPA requested a teleconference with the sponsor to discuss initial concerns identified with the proposed proprietary names for this product.

On the day of the teleconference, January 11, 2010, the sponsor emailed a correspondence that provided a revised order of preference of the previously proposed names submitted on December 16, 2009. This correspondence was pending submission to the NDA application, but had not been submitted at the time of the teleconference. (Please see attachment)

MEETING OBJECTIVES:

The purpose of this meeting was to discuss the sponsor's December 16, 2009 submission and provide guidance regarding the acceptability of the proposed proprietary name, [REDACTED] (b) (4).

DISCUSSION POINTS:

Following introductions, DMEPA took the opportunity to inform the sponsor that they had conducted a review of the proposed name [REDACTED] (b) (4) and wanted to convey concerns identified with the proposed name before proceeding with a full name assessment. Specifically, DMEPA indicated that [REDACTED] (b) (4) would not alleviate the safety concerns previously communicated in the November 9, 2009 denial letter [REDACTED] (b) (4).

[REDACTED] (b) (4). Further, the sponsor was also informed that DMEPA is likely to have similar concerns with the proposed names [REDACTED] (b) (4).

[REDACTED] (b) (4) In addition, DMEPA conveyed to the sponsor the possibility that additional safety concerns or names of concern could be identified during the full name assessment. Based on this, DMEPA indicated that the sponsor could consider conducting a proprietary name safety assessment survey to aid in the selection of a name for this product prior to submitting it to the Agency for review.

The sponsor inquired about the possibility of utilizing tall man letters [REDACTED] (b) (4). [REDACTED] (b) (4) DMEPA replied that the Agency reserves tall man lettering for known postmarketing name confusion pairs and would therefore discourage its use in this case.

The sponsor inquired whether DMEPA would continue to expedite proprietary name reviews for this application as previously communicated during a meeting held on December 9, 2009. DMEPA clarified that because the OND PDUFA date had passed, name reviews no longer

needed to be expedited to accommodate the application's regulatory clock. However, the Agency informed the sponsor that they would continue to communicate issues in a timely manner within their resources, which is done for all sponsors.

Prior to concluding the call, the sponsor clarified that they would not officially submit the correspondence, dated January 11, 2010, which was sent only via email prior to the teleconference. The sponsor noted that they would reconsider their proposed names prior to another submission to request review of a proprietary name.

POST MEETING NOTES:

On January 14, 2010, the sponsor submitted a request to withdraw the December 16, 2009 submission, which requests review of the four additional proposed proprietary names, (b) (4). This correspondence did not include a request to review any additional names, but noted that the sponsor would submit additional names at a later date.



Westpark Corporate Center
4364 South Alston Avenue
Durham, NC 27713-2220 USA
Phone: 919-361-2286
Fax: 919-361-2290
www.cato.com

11 January 2010

Rafel Dwaine Rieves, M.D., Division Director
Division of Medical Imaging and Hematology Products, HFD-160
Office of Oncology Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Central Document Room
5901-B Ammendale Rd.
Beltsville, M.D. 20705-1266

Re: NDA 22-555, Amendment Number: 0024
Sponsor: Photocure ASA
Product: hexaminolevulinate hydrochloride
Submission: Revised order of preference of new proposed proprietary names for hexaminolevulinate hydrochloride

Attention: Thuy Nguyen, Regulatory Health Project Manager

Dear Dr. Rieves:

Reference is made to the following:

- Photocure ASA (Photocure) New Drug Application (NDA) 22-555 submitted on 30 June 2009 for Hexvix in combination with a Karl Storz photodynamic diagnostic cystoscopic system for the detection of papillary bladder cancer
- Request for Proprietary Name Review dated 25 August 2009
- FDA letter of 10 November 2009 titled Proprietary Name Request Unacceptable
- New proposed proprietary names for hexaminolevulinate hydrochloride dated 16 December 2009

On 25 August 2009, Photocure submitted a Request for Proprietary Name Review for Hexvix for NDA 22-555. On 10 November 2009, FDA sent a letter to Photocure which concluded that the proprietary name Hexvix was not acceptable [REDACTED] (b) (4) [REDACTED]. In a submission to NDA 22-555 on 16 December 2009, Photocure provided four proposed proprietary names for FDA's consideration.

Photocure appreciates the chance to work with the FDA in identifying a new proposed proprietary name for hexaminolevulinate hydrochloride, the drug product of NDA 22-555. In this submission, Photocure is submitting an updated and revised order of preference of new proposed proprietary names for hexaminolevulinate hydrochloride.



CONFIDENTIAL

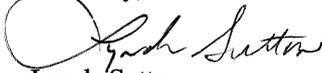
Photocure ASA
Hexvix
NDA 22-555

Cover Letter

Please note that in this updated list of proposed proprietary names, the proposed name [REDACTED] (b) (4) is removed from the first position.

If you have any questions or need additional information, please do not hesitate to contact me by telephone at 919-361-2286 or by fax at 919-361-2290. An Authorization for Regulatory Contact, signed form FDA 356h, and a description of the electronic submission and virus free statement are also enclosed (cover letter attachment).

Sincerely,



Lynda Sutton

Chief Regulatory Officer and US Agent for Photocure

cc: Photocure ASA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

CATHERINE A CARR
01/25/2010



NDA 022555

COMPLETE RESPONSE

Cato Research, Ltd. (for Photocure ASA)
Attn: Lynda Sutton, Chief Regulatory Officer
4364 S. Alston Ave.
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your new drug application (NDA) dated June 30, 2009, received June 30, 2009, submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for Hexaminolevulinate Hydrochloride *Kit* For Intravesical Solution as a part of a combination product in association with the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system, which is the subject of a premarket application (PMA).

We acknowledge receipt of your amendments dated August 20, 25; September 8, 15, 22; October 1, 6, 13, 15, 21, 22, 23, 29; November 4, 9, 19, 20; December 9, 16, 17, and 22, 2009.

We have completed the review of your application and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

REGULATORY

1. Your product, Hexaminolevulinate Hydrochloride *Kit* For Intravesical Solution, is proposed for use in combination with the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system. The Karl Storz D-Light C PDD system is the subject of a PMA, which is currently under review by the Center for Devices and Radiological Health (CDRH). FDA cannot approve your NDA until the PMA for the Karl Storz D-Light C PDD system is approved or otherwise ready for approval. We encourage you to work with the manufacturer of the Karl Storz D-Light C PDD system to obtain marketing approval.

CLINICAL

2. Your proposed product vial packaging and product reconstitution procedures do not sufficiently minimize the risk of medication errors. As described in the proposed labeling, to “mix the contents gently within the syringe,” the healthcare provider must manipulate a 50 or 60-cc syringe with its attached needle still inserted in the vial. The health care provider then holds the syringe/needle and vial while shaking the contents. These procedures and the resulting unstable connection between the needle and vial are not consistent with usual reconstitution procedures. In addition, these procedures promote unintentional needle puncture/sharps-injury to the healthcare provider. For these reasons, redesign the product packaging configuration and product reconstitution procedures to include a more intuitive process in order to minimize the potential for medication errors or sharps-injury to the provider. Specifically:
 - a. Redevelop your product’s reconstitution and preparation process to one that does not involve multiple punctures of the product-powder vial or imply the need for multiple punctures, as may occur with a multi-step reconstitution process. A one step dilution process is preferable and should be supported by the appropriate data. Additionally, the revised process must not involve the use of a needle-appended syringe during the step at which the provider is to “mix the contents gently within the syringe.” Furthermore, your revision should take into consideration any potential failure modes that may occur at all steps of the product reconstitution and preparation process. In addition, as further described in item 4 below, the dilution process should include a method to transfer the final solution to the bladder catheter. Within your submission, include information to support the relationship of the revised dilution-transfer process to, and its consistency with, the process used in the major clinical trials. We encourage a pre-submission meeting to discuss your proposed changes and the appropriate testing to ensure the usability of the revised product packaging configuration and preparation procedures by the appropriate end-users. In developing your system we recommend consideration of principles in the FDA Guidance: *Medical Devices with Sharps Injury Prevention Features*; <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071755.pdf>.
 - b. Revise your proposed package insert to describe the revised product reconstitution and preparation process in a manner that clearly outlines each step. We strongly recommend the use of diagrams to enhance the directions for use.
3. The currently proposed product preparation process involves the use of an unlabeled syringe. Depending upon your proposal in response to item 2 and 4 of this letter, reconfigure your product-powder vial label so that the product information can be transferred from the vial to the syringe or other appropriate system that will contain the final solution for administration into the bladder. This transferable label should contain, at a minimum, the product name, strength/milliliters and route of administration. Within the package insert's description of the product reconstitution process (see above), include this final step for affixing the transferable label to the syringe.

4. Your product's administration procedures are not adequately described within the proposed labeling. At the December 9, 2009 meeting, you demonstrated the procedures involved in injecting your product into the bladder. One procedural step involved the use of tubing labeled solely for the vascular administration of solutions; another procedural step involved the relatively rudimentary “plugging” of a Luer-tipped syringe (without the needle) and/or tubing into the non-conforming urine drainage tip of a bladder catheter. The use of tubing intended solely for intravascular use may increase the risk for vascular injection of your product. The lack of a properly designed connection between the delivery tubing or syringe may result in “spray” or “leakage” of the product and skin contact risks for both the patient and healthcare provider. To optimize the product administration procedures:
 - a. Redevelop the “kit” to contain a bladder catheter with a tip designed specifically to maintain a stable connection between the dilution-transfer system (item 1, above) and the bladder catheter. Alternatively, modify the proposed package insert to identify the specific bladder catheter(s) or catheter characteristics that must be used during the product's administration in order to maintain a stable syringe-bladder catheter connection. These connections must not rely upon manual pressure or necessitate manual manipulation to maintain the connection. Supply information that verifies the compatibility of your reconstituted product with the inner wall of the catheter, connecting tubing and adapter lumens.
 - b. Following administration of your product into the bladder, healthcare providers may apparently either remove the bladder catheter or maintain the catheter in place to prevent inadvertent early elimination of the product. Maintenance of the catheter within the bladder apparently must involve some form of catheter “clamping.” Therefore, in addition to the bladder catheter features described above, the bladder catheter should allow for episodic clamping/occlusion.
 - c. Revise the proposed package insert to explicitly describe all the major steps involved in your product’s administration into the bladder, including the procedures for connecting the Luer-tipped dilution/transfer system to the “in flow” bladder catheter tip. Include the use of diagrams/illustrations to add clarity to the sequential instructions. Explicitly describe whether the bladder catheter may be removed or whether it should remain in place for clamping/occlusion to prevent product elimination. Describe also how the product should be evacuated from the bladder following completion of the necessary retention time.

5. The cystoscopic examination procedure is insufficiently described within the proposed package insert. Certain aspects of your description of the examination procedures at the December 17, 2009 Advisory Committee Meeting appeared to refer to the “switching” between blue and white light during cystoscopy. Conceivably, this “switching” was intended to apply only to procedures performed followed completion of bladder mapping. A "switching" procedure has not previously been proposed as a component of your product's labeling. The lack of sufficient description of the cystoscopic examination procedure increases the risk for misdiagnosis or failed detection of cancer. To address these concerns:
 - a. Revise your proposed package insert to briefly describe the major steps involved in the cystoscopic examination procedure (as performed in the clinical trials) to ensure that all lesions identified by white light, blue light and both lights are appropriately mapped. If you wish to include procedures that involve “switching” between white and blue light, submit the appropriate documentation for consideration for possible inclusion in labeling. Consider the use of bladder maps or other figures/diagrams to enhance the informativeness of the description.
 - b. Proper use of your product involves thorough mapping of the bladder mucosa using white light followed by refinement of the mapping based upon the mucosal appearance with blue light illumination. Within your package insert revision, prominently describe the requisite bladder mapping procedures. Describe any video-mapping options or manual mapping procedures. As a component of labeling, consider the development of a unique procedural manual that, in addition to any other information, provides details of the cystoscopic examination techniques essential for safe and effective use of your product. This procedural document may expand upon summary information within the package insert. Insufficient description of the procedural steps within the package insert may necessitate the development of a unique procedural document as a component of labeling.
 - c. Supply a copy of a “Training Manual” that succinctly describes the use of your product and the essential aspects of cystoscopic examination using the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system. You may wish to combine this “Training Manual” with the procedural manual (cited above) to form a single document that comprises a component of the proposed labeling for your product.
 - d. In the development of your revised labeling, ensure consistency in the information contained between the labeling for your product and the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system.

6. Safety and efficacy data were supplied to support a single administration of your product. In the clinical trial (Study 305) submitted as confirmatory evidence of safety and efficacy, patients had to have a known or suspected bladder cancer, based upon findings from a prior cystoscopy.
 - a. Describe the proposed use of your product in urologic practice and incorporate important aspects of this description into the proposed labeling. Consider the following questions and requests:
 - i. Do you envision the use of your product among patients who have not previously undergone a cystoscopy?
 - ii. How should practitioners use your product if its use is limited to a single administration?
 - iii. Discuss recommendations to assist providers in identification of patients appropriate to receive your product, particularly considering its single use limitation.
 - b. We are particularly concerned about the potential for repetitive administrations of your product, despite labeling that describes its intended “single use.” Describe your plans for subsequent clinical studies that examine the safety and efficacy of repetitive administrations of your product. In general, we regard at least one adequate and well controlled study as essential to establish the safety and efficacy of repetitive product administrations.
7. Based upon our review of your response to the items listed above, additional clinical data may be necessary to assess the safety and efficacy of your product, including aspects related to product reconstitution and administration as well as the cystoscopic procedures.
8. Please be aware that any changes to the drug product formulation, container, closure or other drug contact surfaces (e.g., syringe, catheter, etc.) must be supported by the submission of correspondingly appropriate chemistry, manufacturing, and control (CMC) information and data (e.g., compatibility, stability, in-use testing, etc.). This consideration includes, but is not limited to, changes in the size and materials of construction and the addition of a co-packaged catheter.
9. Regarding our findings from the submitted clinical data, we note that Study 305 was submitted to confirm the safety and efficacy of your product. The desired statistical success was demonstrated for the “detection” co-primary endpoint but not for the “recurrence” co-primary endpoint. Post-hoc, exploratory analyses of the “supportive” studies showed “detection” findings generally consistent with those observed in Study 305. Study 304, the only supportive study that examined “recurrence,” failed to achieve its desired outcome.

- a. Together, these data generally indicate your product may assist in the detection of non-muscle invasive papillary bladder cancer. However, the data do not provide persuasive evidence that this detection results in a reduction of “recurrence.” This observation is based upon the failure to achieve statistical success for the “recurrence” outcomes as well as our inability to rule out uncontrolled bias in Study 305 associated with the open-label aspect of the follow-up period.
- b. Revise your proposed package insert to delete citations to the “recurrence” outcomes.

LABELING

10. Submit draft labeling that incorporates the requested revisions cited above. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

11. Submit draft carton and container labeling revised based upon the requested alterations, as listed above.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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

NDA 022555: Hexaminolevulinate Hydrochloride Kit For Intravesical Solution

Page 8

If you have any questions, contact Thuy M. Nguyen, M.P.H., Regulatory Health Project Manager, at (301) 796-2050 or Thuy.Nguyen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D., Director
Division of Medical Imaging
and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22555	----- ORIG-1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

THUY M NGUYEN
12/30/2009

RAFEL D RIEVES
12/30/2009

FDA - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY DRUG PRODUCTS (DMIHP)

POST AC WRAP-UP INTERNAL MINUTES

NDA: 22-555
DRUG NAME: Hexvix
SPONSOR: Photocure ASA
DATE: Thursday, December 24, 2009

PARTICIPANTS

Siham Biade, Ph.D., Acting P\T Team Leader, DMIHP
Catherine Carr, Regulatory Health Project Manager, OSE
Shaw Chen, M.D., Deputy Director, Office of Non-Prescription Drugs
Young-Moon Choi, Ph.D., Clinical Pharm Team Leader
Melina Griffis, Pharm.D., Team Leader, OSE, DMEPA
Ira Krefting, M.D., Safety Team Leader
Scheldon Kress, M.D., Clinical Reviewer, DMIHP
Patricia Love, M.D., M.B.A., Deputy Director, Office of Combination Products
Thuy Nguyen, M.P.H., Regulatory Health Project Manager, DMIHP
Dwayne Rieves, M.D., Division Director, DMIHP

AGENDA: Post AC Wrap-Up Meeting - To discuss the AC meeting, 12\17\09, and the review status as well as the regulatory action.

AC Results: (9) in favor and (8) not in favor.

CDER recommends an approval action, however, since this is a combination product and CDRH manufacturing inspection will not be completed until March 2010, CDER will issue a Complete Response (CR) regulatory action instead.

Additionally, there are labeling issues (ie, Foley catheter, solution mixture, etc.) among others which will be outlined in the CR letter.

Minutes Recorded By: T.Nguyen, DMIHP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
12/29/2009

MEMORANDUM OF TELEPHONE CONVERSATION

DATE: December 16, 2009

DRUG: hexaminolevulinate hydrochloride solution

NDA: 022555

SPONSOR: Will Lee
Photocure ASA c/o CATO Research, Ltd.

FDA: Catherine Carr, M.S.
Safety Regulatory Project Manager/OSE

Subject: Response to sponsor's correspondence regarding additional proposed proprietary names

On December 16, 2009, the sponsor emailed the OND Regulatory Project Manager, Thuy Nguyen, with the attached correspondence which provides four new proposed proprietary names for hexaminolevulinate hydrochloride as well as additional comments regarding the December 9, 2009 face-to-face meeting between FDA, Cato Research, and Photocure ASA.

After consulting with the Deputy Division Director for DMEPA, a call was placed to the sponsor in response to this correspondence. The sponsor was informed that the full official submission had not yet been received via the document room. Therefore, DMEPA would not be able to provide comments on the contents of the submission nor provide any input on the new proposed proprietary names. Hence, a telephone conference with the sponsor was considered premature and would not be granted. The sponsor was informed that if DMEPA had questions upon review of the submission, they would be contacted at that time.

In light of the sponsor's pending submission regarding the review of four new proprietary names for hexaminolevulinate hydrochloride, it was requested that they withdraw their request for reconsideration of the proposed proprietary name, Hexvix, dated November 20, 2009. The sponsor indicated that they would submit such correspondence to their application to administratively close the Hexvix reconsideration request.

The sponsor was also informed that DMEPA would work to complete the review for the new proposed proprietary names listed in the submission, dated December 16, 2009, working with DMIHP's timeline for regulatory action on the application.

The conversation ended amicably.



Westpark Corporate Center
4364 South Alston Avenue
Durham, NC 27713-2220 USA
Phone: 919-361-2286
Fax: 919-361-2290
www.cato.com

16 December 2009

Rafel Dwaine Rieves, M.D., Division Director
Division of Medical Imaging and Hematology Products, HFD-160
Office of Oncology Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Central Document Room
5901-B Ammendale Rd.
Beltsville, M.D. 20705-1266

Re: NDA 22-555, Amendment Number: 020
Sponsor: Photocure ASA
Product: Hexvix®
Submission: New proposed proprietary names for hexaminolevulinate hydrochloride

Attention: Thuy Nguyen, Regulatory Health Project Manager

Dear Dr. Rieves:

Reference is made to the Photocure ASA (Photocure) New Drug Application (NDA) 22-555 submitted on 30 June 2009 for Hexvix® in combination with a Karl Storz photodynamic diagnostic (PDD) cystoscopic system for the detection of papillary bladder cancer. Reference is also made to the Hexvix Kit Demonstration meeting held on 09 December 2009 between FDA and Photocure.

On 09 December 2009, a face-to-face meeting was held with representatives from Photocure and representatives from the Division of Medical Imaging and Hematology Products, the Division of Medication Error Prevention and Analysis, the Office of Combination Products and the Office of Surveillance and Epidemiology. The purpose of the meeting was to demonstrate the use of the Hexvix Kit. At the conclusion of the meeting, members of the Office of Surveillance and Epidemiology and the Division of Medication Error Prevention and Analysis indicated their willingness to review new proprietary names from the sponsor in time for the Action Date of 30 December 2009.

Photocure appreciates the chance to work with the FDA in identifying a new proposed proprietary name for hexaminolevulinate hydrochloride, the drug product of NDA 22-555. Please find below a list of four proposed proprietary names for hexaminolevulinate hydrochloride in order of preference:



Cover Letter

In order to expedite the process, Photocure kindly asks that a telephone conference be scheduled with the FDA, if possible this week (either on Wednesday, 16 December 2009 or Friday, December 2009) to discuss the proposed names and agree on Photocure's formal submission for a Request for Proprietary Name Review.

If you have any questions or need additional information, please do not hesitate to contact me by telephone at 919-361-2286 or by fax at 919-361-2290. An Authorization for Regulatory Contact, signed form FDA 356h, and a description of the electronic submission and virus free statement are also enclosed (cover letter attachment).

Sincerely,



Lynda Sutton
Chief Regulatory Officer and US Agent for Photocure

Enclosures

cc: Photocure ASA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

CATHERINE A CARR
12/18/2009

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, the FDA has the following CHEMISTRY Information Request – December 10, 2009.

By 12:00 pm, EST, Monday, December 14, 2009, provide a response to me via email: Thuy.Nguyen@fda.hhs.gov, and follow-up with an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22-555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA CHEMISTRY INFORMATION REQUEST

Regarding NDA 22-555 (Hexvix), submission dated June 30, 2009, the FDA has the following Chemistry comments and information request:

CMC Label Comments

Provide Container and Carton labels taking into account the following comments:

1. Be advised that the product, in the absence of acceptable trademark, will be labeled as “Hexaminolevulinate Hydrochloride for Intravesical Solution”. If a trademark is accepted then the product will be labeled as “Trademark (hexaminolevulinate hydrochloride) for Intravesical Solution”. Accordingly, following labeling will be used for different product components:

Kit Label:

“Hexaminolevulinate Hydrochloride *Kit* for Intravesical Solution”, or
Trademark (hexaminolevulinate hydrochloride) *Kit* for Intravesical Solution”.

Powder Vial Label:

“Hexaminolevulinate Hydrochloride for Intravesical Solution”, or
Trademark (hexaminolevulinate hydrochloride) for Intravesical Solution”.

FDA CHEMISTRY INFORMATION REQUEST (cont.)

DILUENT Vial Label:

“DILUENT for Hexaminolevulinate Hydrochloride”, or
“DILUENT for Trademark”

2. We again recommend that you use following storage statements for kit and individual vials.

Kit:

“Store at controlled room temperature of 20° - 25°C (77°F)”

Vials:

(b) (4)

3. The peel-off label to be placed on powder vial should include the following information:
 - a. Reconstituted product identity
 - b. Statement “For Bladder Instillation Only”
 - c. Statement for product storage
 - d. Statement for product expiry.
4. Include quantitative content statements on all product components (kit and vials) as requested in previously sent comments per 21CFR 210.10(d)(1).

NOTE: For the purpose of the label revisions, besides a narrative response, submit the above revisions also as a MS Word and PDF.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
12/10/2009

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, the FDA has the following STATISTICAL Information Request – December 10, 2009.

By 12:00 pm, EST, Friday, December 11, 2009, provide a response to me via email: Thuy.Nguyen@fda.hhs.gov, and follow-up with an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22-555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA STATISTICAL INFORMATION REQUEST

Regarding NDA 22-555 (Hexvix), submission dated June 30, 2009, the FDA statistical reviewer, Dr. Anthony Mucci, has the following statistical information request:

In the Detection Group of 286 confirmed Ta/T1 subjects:

(1): How many subjects satisfied both of the following conditions:

(A): There was at least one confirmed Normal detected by Blue Light that was not detected by White Light

(B): Blue Light found no Ta/T1's missed by White Light

Also:

(2): How many subjects satisfied all of the following conditions:

(A): There was at least one confirmed Normal detected by Blue Light that was not detected by White Light

(B): Blue Light found no Ta/T1's missed by White Light

(C): White Light had no Normal detections

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
12/10/2009

***CONFIDENTIAL**

FDA - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY DRUG PRODUCTS (DMIHP)

IND INDUSTRY MEETING MINUTES

NDA: 22-555

DRUG NAME: Hexvix

SPONSOR: Photocure, ASA

DATE: Wednesday, December 9, 2009, at 1:30 pm

LOCATION: WO #22 – Conf Room 1417

SPONSOR PARTICIPANTS

In-Person

Allen Cato, MD, PhD, President, Cato Research
Andrew Daleus, Project Manager, Cato Research
Susan Elliott, Senior Manager, Regulatory Labeling and Compliance, GE Healthcare
Lynda Sutton, US Regulatory Agent for Photocure, Cato Research
Elaine Wright, GE Healthcare

Via Teleconference

Inger Ferner Heglund, MSc, Head of R&D
Ingunn Munch Lindvig, PhD, Director of Regulatory Affairs

(b) (4)

Yngvil Kloster Thomas, MSc, Project Director
Gry Stensrud, Ph.D., Pharmaceutical Director

FDA PARTICIPANTS

Kristina Arnwine, Pharm.D., Team Leader, Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE)
Catherine Carr, Pharm.D., Project Manager, OSE
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader, Div of Medical Imaging and Hematology Products (DMIHP)
Anne Crandall, Pharm.D., Safety Evaluator, OSE
Alex Gorovets, M.D., Clinical Team Leader, DMIHP
Melina Griffis, Pharm.D., Team Leader, DMEPA, OSE
Carol Holquist, Pharm.D., Director, DMEPA, OSE
Ravi Kasliwal, Ph.D., Chemistry Reviewer, DMIHP
Scheldon Kress, M.D., Clinical Primary Reviewer, DMIHP
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead, DMIHP

NDA 22-555: Hexvix

Page 2

FDA PARTICIPANTS (cont.)

Richard Lostritto, Ph.D., Division Director, Office of New Drug Quality Assurance (ONDQA)

Patricia Love, M.D., Deputy Director, Office of Combination Products

Thuy Nguyen, M.P.H., Regulatory Health Project Manager, DMIHP

Rafel Dwaine Rieves, M.D., Division Director, DMIHP

Tselaine Jones Smith, Pharm.D., Safety Evaluator, DMEPA, OSE.

Denise Toyer, Pharm.D., Deputy Director, DMEPA, OSE

Jyoti Zalkikar, Ph.D., Statistical Team Leader, DMIHP

AGENDA: Type A meeting for the Sponsor to demonstrate the use of the Hexvix Kit as well as to discuss the FDA's concerns with the proprietary drug name.

Prior to the Sponsor's demonstration of the Hexvix Kit, the FDA informed the Sponsor that the preliminary recommendation for the regulatory action of the NDA would be a Complete Response (CR) due to the issues with the CDRH PMA manufacturing inspection.

Following the Sponsor's video and demonstration of the Hexvix Kit, the following discussion ensued:

The Sponsor will identify a US approved transfer adaptor (device) that can be connected to the intravesical tube part of the Foley catheter to insert the Luer Lock syringe for the Hexvix solution administration.

The FDA noted that while the proposed insert for the product directs insertion of the syringe with the diluent into the Hexvix powder [REDACTED] (b) (4)

[REDACTED]. FDA asked the Sponsor the reason for the difference to which the Sponsor explained that that is the current practice in Europe for the reconstitution to ensure that all the powder is dissolved and transferred out of the vial. The Sponsor does not have any specific reason for [REDACTED] (b) (4)

[REDACTED] the administration of the reconstitution and instillation, however, no monitoring was conducted during the reconstitution and administration of the drug.

The FDA asked if the nurses or technicians in the urological suites were trained during the clinical trials to perform the reconstitution to which the Sponsor explained that instructions were provided.

NDA 22-555: Hexvix
Page 3

The FDA stated that the labeling should describe whether or not to leave in place or remove the catheter following administration of Hexvix solution, to which the Sponsor explained that in European clinical setting, sometimes the catheter was removed and other times it was left in. The Sponsor will provide in the labeling, a pictorial description of the solution insertion into the catheter.

With regards to the syringe, the Sponsor agreed to condense the vial text (to include the drug name, route of administration, and storage) and provide a transferable peel-off label. Also, the Sponsor will provide the NDC # for the Kit containing diluent in the glass vial. The FDA will forward to the Sponsor additional chemistry labeling and label comments.

Regarding the Sponsor's rebuttal of the proprietary name, submission dated 11/20/09, the FDA stated that the proprietary name – Hexvix, is unacceptable and explained that the lack of reporting of errors is not the same as the lack of error occurrence. Also, the FDA stated that the usage system in the US is not the same as Europe – there is a lack of uniformity and consistency. The FDA stated that errors may occur in misadministration (not just due AEs), packaging, or ordering the drug. The FDA – Office of Surveillance and Epidemiology (OSE), will issue the Sponsor a letter by December 30, 2009, in response to the submission dated 11/20/09.

ACTION ITEMS

1. The FDA will forward to the Sponsor additional chemistry labeling & label comments and the Sponsor will provide the NDC #, discussed above.
2. If available, the Sponsor will provide 510K PMA number for the US approved Foley adaptor.
3. FDA – OSE will issue a letter by 12/30/09, in response to the submission dated 11/20/09.

Meeting Minutes Recorded By: T.Nguyen, DMIHP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22555	----- ORIG-1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

THUY M NGUYEN
12/24/2009

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, the FDA has the following comments regarding the Hexvix Kit demonstration at today's meeting – December 9, 2009.

If you have any questions, please feel free to contact me.

FDA COMMENTS

1. How do you connect the syringe to a bladder catheter?
2. Are any special gauge needles required for drug reconstitution?
3. Are any special drug disposal considerations?
4. Who is anticipated to reconstitute the drug and where is it to be reconstituted?
5. Are gloves required during reconstitution and all handling of the drug?
6. Clarify the use of the PDD system/can the mode 3 setting be used for cystoscopy.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
12/09/2009

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FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, the FDA has the following STATISTICAL Information Request – December 9, 2009.

By 9:00 am, EST, Thursday, December 10, 2009, provide a response to me via email: Thuy.Nguyen@fda.hhs.gov, and follow-up with an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22-555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA STATISTICAL INFORMATION REQUEST

Regarding NDA 22-555 (Hexvix), submission dated June 30, 2009, the FDA statistical reviewer, Dr. Anthony Mucci, has the following statistical information request:

Confirm the statistics derived from the data sets:

(1): At subject level, for detection: 38 of the 286 subjects had at least one Normal detected by Blue Light but not by White Light

(2): At subject Level, for detection, and for subjects with exactly one confirmed Ta/T1 Lesion:

There were 105 such subjects (out of the 286)
Both Blue & White detected this Lesion in 91 subjects
White alone detected it in 11 subjects
Blue alone detected it in 3 subjects

(3): At subject Level, for detection, and for subjects with exactly one confirmed Normal Lesion:

There were 55 such subjects (out of the 286)
Both Blue & White detected this Lesion in 26 subjects
White alone detected it in 8 subjects
Blue alone detected it in 21 subjects

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22555	----- ORIG-1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

THUY M NGUYEN
12/09/2009

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, the FDA has the following CLINICAL Information Request – December 7, 2009.

By 12:00 pm, EST, Tuesday, December 8, 2009, provide a response to me via email: Thuy.Nguyen@fda.hhs.gov, and follow-up with an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22-555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA CLINICAL INFORMATION REQUEST

Regarding NDA 22-555 (Hexvix), submission dated June 30, 2009, the FDA has the following Clinical Information Request:

1. In relation to the 13 patients in the Hexvix group who did not undergo blue light cystoscopy, clarify whether any lesions were mapped (or biopsied and/or removed), following the randomization into this group, in addition to the lesions mapped prior to such randomization? Provide the appropriate CRFs to support your clarification.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22555	----- ORIG-1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

THUY M NGUYEN
12/07/2009

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, the FDA has the following CHEMISTRY Information Request – December 3, 2009.

By 12:00 pm, EST, Monday, December 7, 2009, provide a response to me via email: Thuy.Nguyen@fda.hhs.gov, and follow-up with an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22-555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA CHEMISTRY INFORMATION REQUEST

Regarding NDA 22-555 (Hexvix), submission dated June 30, 2009, the FDA has the following Chemistry comments and information request:

CMC Comments

1. Periodic testing for tests listed as part of drug substance and drug product specifications is not acceptable. Testing for all attributes listed under specifications must be conducted for all batches to release the batch.
2. Clarify whether you intend to market the DILUENT for Hexalevulinate Hydrochloride in the glass bottle, (b) (4) polypropylene bottle or both. Also, clarify if the NDC numbers for the kits containing glass bottles and the (b) (4) bottles will be the same.
3. Provide amended post-approval stability protocol for Hexvix powder vials which indicates that the first three commercial batches will also be placed on long term stability. This is because the stopper coating formulation has changed and the primary stability data is from the previously used coating.
4. Describe details of the *kit* carton, e.g., how the vials are held together in the *kit*. Consideration should be made to physically linking the drug vial and DILUENT together in some manner (e.g. plastic ring). Having vials physically linked will lessen the likelihood of storage of the drug and DILUENT in different places and inadvertently using a different DILUENT.

FDA CHEMISTRY INFORMATION REQUEST (cont.)

CMC Comments

5. In the section 2.1 of the package insert, in addition to providing the written details of the dilution process, include a pictorial description of the dilution and administration process. Additionally, in the written section include details for the instillation of drug product into the bladder.
6. Provide amended carton, container and vial labels (as a MS Word Doc and PDF) that incorporate the following:

Label Comments For Container and Carton

- Since trademark Hexvix is not acceptable, place established name of the drug along with the dosage form “Hexaminolevulinate Hydrochloride for Intravesical Solution”, all in the same letter size in the same line, as the name of the drug on the powder vial.
- Revise and place the strength as (b) (4) underneath the established name statement.
- Place statement (b) (4) prominently underneath the strength statement.
- Revise the caution statement (b) (4) to read, (b) (4) and place it prominently below the (b) (4) statement.
- Increase prominence of the “Rx Only” statement.
- Place statement “Sterile”, opposite to the NDC code above the name of the drug.
- Place statement (b) (4) in the same line.
- Include content statement, “(b) (4),” on the powder vial label.
- Place the title statement “Dosage and Administration” under the contents statement, and revise its content as follows:

(b) (4)

- Revise the storage statement to read:
(b) (4)

Additionally, since the final administered product will be in a syringe, the hexaminolevulinate powder vial should contain transferable features, so that the label could be peeled off by the end user from the vial and affixed to the syringe. Include following on this label:

FDA CHEMISTRY INFORMATION REQUEST (cont.)

Label Comments For Container and Carton (cont.)



Label Comments For Diluent For Hexaminolevulinate Hydrochloride Vial

- Revise the name for “Solvent for Hexvix” to “**DILUENT** for Hexaminolevulinate Hydrochloride”. The word **DILUENT** should be more prominent than “for Hexaminolevulinate Hydrochloride” wording.
- Place the volume amount to “50 mL” underneath (b) (4)
- Place statement (b) (4) prominently underneath the volume statement.
- Revise the contents statement to read (b) (4)
- Replace statement (b) (4) and place it under the contents statement (leave space).
- Place statement (b) (4) under above statement.
- Increase prominence of the “Rx Only” statement.
- Place statement “Sterile”, opposite to the NDC code above the name of the drug.
- Place statement (b) (4) in the same line.
- Revise the storage statement to read: (b) (4)
- The color scheme for the DILUENT vial label should be clearly different than for the hexaminolevulinate hydrochloride for intravesical solution vial to allow for ready distinction.

FDA CHEMISTRY INFORMATION REQUEST (cont.)

Label Comments For Hexaminolevulinate Hydrochloride *KIT* For Intravesical Solution

- Revise the established name from “HEXVIX™” to “Hexaminolevulinate Hydrochloride *Kit* for Intravesical Solution” all in same letter size and on same line. the word “*Kit*” should be differentiated from other wording. Additionally, remove statement (b) (4) from the carton label.
- Revise and place the strength as “100 mg” underneath the established name.
- Place statement (b) (4) prominently in bold underneath the strength statement.
- Place following statement it below the “(b) (4)” statement in the front and back panel of the carton label:

(b) (4)

- Revise the caution statement (b) (4) and place it prominently below (b) (4) the front and back panel.
- Increase prominence of the (b) (4) statement.
- Place statement (b) (4) in the same line.
- Revise the contents statement on the Top panel as follows:

(b) (4)

- The title statement “Dosage and Administration” should be placed under the content statement.
- Place statement “(b) (4)” first under Dosage and Administration.
- Place statement (b) (4) under above statement.
- Revise and place the following instructions below the above dosage statement:

(b) (4)

- Revise and place the storage statement on the top and side panel:
(b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
12/03/2009

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, the FDA has the following STATISTICAL Information Request – December 2, 2009.

By 12:00 pm, EST, Thursday, December 3, 2009, provide a response to me via email: Thuy.Nguyen@fda.hhs.gov, and follow-up with an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22-555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA STATISTICAL INFORMATION REQUEST

Regarding NDA 22-555 (Hexvix), submission dated June 30, 2009, the FDA statistical reviewer, Dr. Anthony Mucci, has the following statistical information request:

1. The statistical reviewer cannot find primary statistics on detection and recurrence by age/race/gender. Please direct us to the appropriate sections of the submission, and, additionally, please send tables separately.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
12/02/2009

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, the FDA has the following STATISTICAL Information Request – November 16, 2009.

By 12:00 pm, EST, Tuesday, November 17, 2009, provide a response to me via email: Thuy.Nguyen@fda.hhs.gov, and follow-up with an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22-555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA STATISTICAL INFORMATION REQUEST

Regarding NDA 22-555 (Hexvix), submission dated June 30, 2009, the FDA has the following statistical information request:

Please provide the table below for the Primary Detection Endpoint:

	# Centers	Median Center Size	# Subjects	#Subjects BL>WL	% BL>WL
Overall			286	47	16%
US/Canada					
Europe					

The “Overall” row, of course, contains the Primary Endpoint results.

Note: BL>WL means Blue Light found a Ta/T1 missed by White Light

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22555	----- ORIG-1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

THUY M NGUYEN
11/16/2009

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com

Regarding NDA 22-555: Hexvix, submission dated June 30, FDA the FDA has the following PHARMACOLOGY\TOXICOLOGY Information Request – November 10, 2009. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA PHARMACOLOGY\TOXICOLOGY COMMENTS

Regarding NDA 22-555 (Hexvix), submission dated June 30, 2009, the FDA has the following pharm/tox comments:

The FDA has completed the review of the genotoxicity studies submitted. We concluded that the genotoxicity studies were adequately conducted in the absence of light exposure and the findings will be used in the labeling. However, all in vitro genotoxicity studies in the presence of visible light (Study 1555/30-D6171, Ames assay; Study 1555/29-D6172, chromosome Aberrations assay in CHO cells; Study 7505-100, mouse lymphoma assay) were not adequately conducted because the studies in the presence of S9 and the confirmatory studies when the results were negative were not conducted. Therefore, genotoxicity in the presence of light exposure is not adequately evaluated. The information derived from these studies cannot be used in the labeling.

We also reviewed the comet assay which was conducted using tissues from the local tolerance study in dogs. However, this study was not adequately conducted because of deficiencies such as using only two animals per time points and no positive controls included (which made data interpretation rather difficult). In addition, the time points used for the analysis were too late (Day 3 as the earliest time point). In general, samples are collected at 3 and 24 h post doing). Therefore, the information derived from this study cannot be used in the labeling as well.

We recommend the following labeling for hexaminolevulinate hydrochloride regarding the genotoxicity potential in the presence of light exposure: “adequate genetic toxicity studies have not been performed to evaluate the genetic toxicity of hexaminolevulinate hydrochloride in the presence of light exposure.”

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
11/10/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 022555

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Photocure ASA
c/o CATO Research, Ltd.
Westpark Corporate Center
4364 South Alston Avenue
Durham, NC 27713

ATTENTION: Lynda Sutton, B.S.
Chief Regulatory Officer

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) dated June 30, 2009, received June 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hexaminolevulinate Hydrochloride, 100 mg for bladder instillation.

We also refer to your August 25, 2009, correspondence, received August 25, 2009, requesting review of your proposed proprietary name, Hexvix. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons.

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the draft Guidance for Industry, *Complete Submission for the Evaluation of Proprietary Names*, [HTTP://www.fda.gov/cder/guidance/7935dft.pdf](http://www.fda.gov/cder/guidance/7935dft.pdf) and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Catherine Carr, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2311. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Thuy Nguyen at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

CAROL A HOLQUIST
11/09/2009

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FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, the FDA has the following STATISTICAL Information Request – November 5, 2009.

By 3:00 pm, EST, Friday, November 6, 2009, provide a response to me via email: Thuy.Nguyen@fda.hhs.gov, and follow-up with an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22-555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA STATISTICAL INFORMATION REQUEST

Regarding NDA 22-555 (Hexvix), submission dated June 30, 2009, the FDA statistical reviewer, Dr. Anthony Mucci, has the following statistical information request:

Statistical Reviewer Clarification Request

First, the Detection Endpoint:

My Understanding concerning the Co-Primary Endpoint(1):

To test if the proportion of Group B patients with confirmed Ta/T1 lesions found by Blue Light and not by White Light exceeds 10%.

In your Statistical Report:

I'll paraphrase from **Section 7.4.1 p44 of 75**: "This was tested by a two-tailed test at the 1% level using an exact test. The resulting p-value was $p = .001$. Hence the result was statistically significant."

In the same paragraph you further state:

(1): "A 99% CI for this proportion is (11.2% , 22.*%)"

(2): " ... it was concluded that the proportion of patients is above 10%."

FDA STATISTICAL INFORMATION REQUEST (cont.)

However, the actual hypotheses are: (Paraphrase from Section 5.5.1.3 p21 of 75):

Null: $P = 10\%$ versus Alternative: $P \neq 10\%$

If your test leads to rejection of the Null at .01, the conclusion would be:

$P \neq 10\%$, not: $P > 10\%$.

My inference is that your conclusion that Proportion $> 10\%$ is drawn (implicitly) from the following logic:

Rejection of pre-specified Null

Followed by

Examination of Lower Limit of the 2-sided 99% CI (LL = 11.2%).

1. Is my inference correct? If so, then it appears that your success criterion is implicit (Rejection of Null followed by, presentation of CI's) rather than pre-specified.

I'm assuming you actually wanted to test:

**** Null: $P \leq 10\%$ versus Alternative: $P > 10\%$***

*My assumption is that a test of *, using, say, one-sided CI's determined, say, from normal approximations for P, would yield LL's of 99% 2-sided CI's in excess of 10%. In this framework the conditions for concluding $P > 10\%$ would be pre-specified instead of implicit, and the $LL > 10\%$ would constitute proof of Superiority to 10%..*

2. Please clarify your logic in drawing your conclusion that $P > 10\%$.

FDA STATISTICAL INFORMATION REQUEST (cont.)

Next, the Recurrence Endpoint:

Statistical Analysis Plan: Section 8.1.2 : Co-Primary Endpoint 2

You state:

“ The Cochran-Mantel-Haenszel Chi-Square Test with center as stratification factor and a significance level of 1% (2-sided) will be used for the confirmatory analysis of the second primary endpoint.”

You also state, in the **Clinical Study Report, Section 9.7.1.4 (Methods of Analysis), P44** (My notation follows):

Null Hypothesis for Recurrence: $P_{\text{White}} = P_{\text{Blue}}$ versus $P_{\text{White}} \neq P_{\text{Blue}}$
Page 2 of 3

Again, my inference here is that you are not testing directly for Superiority, as would be the case if the hypotheses were:

Null Hypothesis for Recurrence: $P_{\text{White}} \leq P_{\text{Blue}}$ versus Alternative $P_{\text{White}} > P_{\text{Blue}}$

So, when you display 2-sided 99% CI's for the **Relative Reduction** of recurrences, along with p-values, the p-values are the direct evidence relevant to the Mantel etc Test, while the Relative reduction CI's are intended only as supportive of trends.

3. Is this correct?

Finally: A Request for Data:

4. Provide numbers and percentages for types of Recurrences (By Arm: White and Blue):

Recurrence is Ta/T1
Recurrence is CIS
Recurrence is Dysplasia
Recurrence is T2/T4

If there is anything above that requires a teleconference for clarification, please let us know.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22555	----- ORIG-1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

THUY M NGUYEN
11/05/2009

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, FDA Clinical Information Request and Sponsor Clinical Response dated November 3, the FDA has the following CLINICAL Information Request – November 4, 2009.

By 12:00 pm, EST, Thursday, November 5, 2009, provide a response to me via email: Thuy.Nguyen@fda.hhs.gov, and follow-up with an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22-555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA CLINICAL INFORMATION REQUEST

Regarding NDA 22-555 (Hexvix), submission dated June 30, 2009, FDA clinical information request and Sponsor clinical response dated November 3, the FDA has the following clinical information request:

1. We are concerned about the possibility of administering Hexvix to an unsuspecting patient with Porphyria and then cystoscoping the patient with blue light. We are trying to anticipate what might be the outcome. Could the entire bladder light up pink-red? Would the patient be at higher risk for a hypersensitivity or anaphylaxis reaction? We realize these are theoretical possibilities, but they are real safety concerns. Please address.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22555	----- ORIG-1	----- PHOTOCURE ASA	----- HEXVIX

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THUY M NGUYEN
11/04/2009

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FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, 2009, the FDA has the following CLINICAL Information Request – November 3, 2009.

By 3:00 pm, EST, Tuesday, November 3, 2009, provide a response to me via email: Thuy.Nguyen@fda.hhs.gov, and follow-up with an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22-555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA CLINICAL INFORMATION REQUEST

Regarding NDA 22-555 (Hexvix), submission dated June 30, 2009, the FDA has the following clinical information request:

1. Please clarify the reason for the proposed contraindication in patients with porphyria.
2. Does it apply to all porphyrias?
3. As many patients with porphyria are not aware that they have this condition, what might possibly happen to a patient with porphyria, if he or she is unknowingly exposed to Hexvix and cystoscoped with blue light?
4. What are the safety implications?

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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THUY M NGUYEN
11/03/2009

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FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, 2009, the FDA has the following CLINICAL Information Request – November 2, 2009.

By 3:00 pm, EST, Tuesday, November 3, 2009, provide a response to me via email: Thuy.Nguyen@fda.hhs.gov, and follow-up with an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22-555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA CLINICAL INFORMATION REQUEST

Regarding NDA 22-555 (Hexvix), submission dated June 30, 2009, the FDA has the following clinical information request:

1. Clarify the proposed Adverse Reactions section of the labeling:



- The proposed labeling does not clearly differentiate the frequency at each timepoint.
- The proposed labeling is not compatible with the events and frequency described in Table 2.7.4-16b in the Summary of Clinical safety
- Where is the data in Table 1 in the labeling derived from?

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
11/02/2009

FDA - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY DRUG PRODUCTS (DMIHP)

INTERNAL MINUTES

NDA: 22-555

DRUG NAME: Hexvix

SPONSOR: Photocure ASA

DATE: Wednesday, September 30, 2009, at 12:00 pm

PARTICIPANTS

Joshua Pfefer, PhD., Reviewer, Center for Devices and Radiological Health (CDRH)
Alex Gorovet, M.D., Clinical Team Leader, DMIHP
Ravi Kasliwal, Ph.D., Chemistry Reviewer, DMIHP
Anthony Mucci, Ph.D., Statistical Reviewer, DMIHP
Thuy Nguyen, M.P.H., Regulatory Health Project Manager, DMIHP
Yanli Ouyang, Ph.D., Pharm\Tox Reviewer, DMIHP

AGENDA: Team Meeting – To discuss the review status and timeline as well as upcoming meetings (ie, PeRC, Mid-Cycle, and AC).

Review Status

- 1. Pharm\Tox:** The Sponsor submitted a new genotoxic study (which the FDA did not request). Review is ongoing and awaiting Sponsor's response to the P\T comments outlined in the Filing Letter, 09\11\09.
- 2. Chemistry:** Under (b) (4) (Hexvix), review was fine so do not anticipate issues with the current NDA. Manufacturing inspection may or may not take place since it already took place (b) (4). Chemist will follow-up on the inspection.
- 3. Clinical:** Review is ongoing and is aware of OSE's concerns regarding the tradename. Also, an Information Request (IR) will be forwarded to the Sponsor regarding the adverse events.
- 4. Statistical:** Review recently began at the end of September. Plans to complete primary and secondary reviews by December 7, 2009.
- 5. PK:** There is no new information to review, but will be involved with the labeling.

Review Status (cont.)

6. Micro: The micro section has not changed [REDACTED] (b) (4), which micro recommended an approval. Do not anticipate any issues and will complete review by due date.

7. CDRH: Although the indication for use has changed [REDACTED] (b) (4) the KSEA device has not changed. CDRH just received P050027/A18 from KSEA concerning the request of quantitative and scientifically-valid evidence to demonstrate that the radiant threshold for the damage potentially caused by Karl Storz D-Light C PDD system with Hexvix® would be significantly lower than the damage threshold found by Vaucher et al., in the study. CDRH has not yet reviewed the European guidelines for Hexvix. Once the data received is reviewed, may want to look more closely at the EU guidelines for the for Hexvix.

Regulatory Recommendation: Tentative approval – pending completion of review.

Upcoming Meetings: PeRC, Mid-Cycle, and AC as well as internal team/labeling meetings along with the AC practices – Check Outlook calendar.

ACTION ITEMS

1. The Project Manager (PM) will revise the timeline since the stat team will not be able to complete their review in November (but, rather by December 7, 2009), and will forward the revised timeline to the Team.
2. The PM will schedule the team/labeling as well as the AC practices.

Minutes Recorded By: T.Nguyen, DMIHP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
10/22/2009

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, 2009, the FDA has the following Label Information Request – October 21, 2009.

By 3:00 pm, EST, today, October 21, 2009, please forward to me via email: Thuy.Nguyen@fda.hhs.gov, the proposed carton and vial labels without the text codes (originally submitted June 30, 2009) as an MS Word Doc, and follow-up with a cover letter of the email response as an official response submission to the NDA via Gateway / GSR electronic submission, as with all submissions regarding NDA 22-555.

If you have any questions, please feel free to contact me.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
10/21/2009

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FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, 2009, the FDA has the following CLINICAL Information Request – October 15, 2009.

By 12:00 pm, EST, Friday, October 16, 2009, provide an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22-555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA CLINICAL INFORMATION REQUEST

Regarding NDA 22-555 (Hexvix), submission dated June 30, 2009, the FDA has the following clinical information request:

1. The false positive rate on a lesion basis was considerably higher in Study 304 than in 305 among all patients, but especially among patients in the Hexvix Group;

Study	Hexvix Group		WL Group
	Blue Light	White Light	
304	55%	30%	32%
305	12%	11%	10%

Do you have an explanation as to why the false positive rate was higher in Study 304? Do you have an explanation as to why the false positive rate was 55% when blue light cystoscopy was performed following TRUB with white light?

2. Are you aware of the standard of practice in Europe as relates to the order of performing biopsies during TRUB when Hexvix is utilized? Do urologists perform their initial series of biopsies after WL or BL or after both? Does performance of biopsies with WL before visualization with BL play a role in reducing the ability to discriminate pathological from normal tissues? Does performance of biopsies with WL before visualization with BL distort the operative field so as to reduce the operators ability to distinguish between normal and abnormal tissues?

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22555	----- ORIG-1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

THUY M NGUYEN
10/15/2009

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FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, and the teleconference of October 15, at 12:00 – 2:00 pm, US EST, the following are FDA additional statistical discussion points (not for implementation) – October 13, 2009.

If you have any questions, please feel free to contact me.

FDA STATISTICAL INFORMATION REQUEST

The following are FDA statistical comments dated 10\13\09, from the statistical reviewer, Dr. Anthony Mucci, in preparation for the teleconference:

I am having difficulty verifying your statistical results; it is conceivable that I am not understanding the data sets. I need to talk with the stat and programming people with both sides in front of the respective computers so that we can go through the definitions and some calculations. I have been examining the following data sets:

SEND.CNTRITT and SEND.CNTRLES_ITT.

FDA STATISTICAL DISCUSSION POINTS dated October 13, 2009

The following are statistical discussion points from the FDA statistical reviewer, Dr. Anthony Mucci, 10\13\09, for the teleconference, 10\15\09:

My main problems are:

(1): For the “lesion level” data, where the rows are lesions (**CENTRLES_ITT**):

I reduced the data set to include only **Ta**, **T1**, and Benign lesions. Once I effected this reduction, I examined, for instance, the variable **TaT1_wb**, subject to the restriction that the variable **PRTYPE** registered as **Ta** or **T1**. In this context, **TaT1_wb** should register as = 1, since the lesion was confirmed as **Ta** or **T1** by histology, according to **PRTYPE**, and the specimen wouldn't have been available for histology if White Light and/or Blue Light didn't detect it. But, the variable **TaT1_wb** sometimes registers = 0 in this scenario, implying that neither diagnostic saw the lesion. How can this be?

FDA STATISTICAL DISCUSSION POINTS dated October 13, 2009 (cont.)

(2): Again, using the subset of **CENTRLES_ITT** consisting of Ta, T1 and benign lesions, I find:

Benign = 137 ; # Ta Lesions = 566 ; # T1 Lesions = 134.

In the submission, Section 7.4.1, Table 16, Photocure lists :

Ta Lesions = 580 ; # T1 Lesions = 95 (I can't find # Normals in the submission.)

FDA ADDITIONAL STATISTICAL DISCUSSION POINTS - October 14, 2009

Table(1)

Lesions means the number of Validated Ta or T1 Lesions found in a subject.
Thus, Lesions = 2 means exactly two Ta and/or T1 lesions were validated for the subject.

Subjects = Number of Subjects with exactly the indicated number of Ta and/or T1 lesions validated by Histology. Thus, in the example, there were 25 subjects with exactly two such lesions, and consequently exactly 50 lesions under #Lesions.

#B&W = Number of such lesions detected by both Blue Light and White Light
B not W = Number of Lesions detected by Blue Light but not by White Light
W not B = Number of Lesions detected by White Light but not by Blue Light

Note in the example the three last columns must add to 50

For the cut-off: Lesions > 3 , there is no obvious relation between # Subjects and # Lesions, but # Lesions = #B&W + #B not W + #W not B

Histology Validated Positive Lesions (Type Ta and/or T1)					
Lesions	#Subjects	# Lesions	#B&W	# (B not W)	# (W not B)
1					
2	25	50	30	15	5
3					
>3	50	200			

FDA ADDITIONAL STATISTICAL DISCUSSION POINTS – October 14, 2009

Table(2)

Lesions means the number of Negative Lesions validated by Histology in a subject. Thus, Lesions = 2 means exactly two Negative lesions were validated for the subject.

Subjects = Number of Subjects with exactly the indicated number of Negative Lesions

#B&W = Number of such lesions detected by both Blue Light and White Light
(False Positives for both)

B not W = Number of such Lesions detected by Blue Light but not by White Light
(False Positive for Blue Light but not for White Light)

W not B = Number of Lesions detected by White Light but not by Blue Light
(False Positive for White Light but not for Blue Light)

Again: # Lesions = #B&W + #B not W + #W not B

Histology Validated Negative Lesions					
Lesions	#Subjects	Total # Lesions	#B&W Lesions	# (B not W) Lesions	# (W not B) Lesions
1					
2					
> 2					

The indicated tables should be generated for:

The entire set of ITT subjects

USA and Not-USA ITT subjects separately

Large Center versus Small Center ITT subjects separately

The Cut-off for Large versus Small will be discussed during the TCON, 10\15\09.
Also, the # Lesions Cut-off (>3 , > 2, etc) will also be discussed.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22555	----- ORIG-1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

THUY M NGUYEN
10/14/2009

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FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, and the teleconference of October 15, at 12:00 – 2:00 pm, US EST, the following are FDA statistical discussion points – October 13, 2009.

If you have any questions, please feel free to contact me.

FDA STATISTICAL INFORMATION REQUEST

The following are FDA statistical comments, 10\13\09, from the statistical reviewer, Dr. Anthony Mucci, in preparation for the teleconference:

I am having difficulty verifying your statistical results; it is conceivable that I am not understanding the data sets. I need to talk with the stat and programming people with both sides in front of the respective computers so that we can go through the definitions and some calculations. I have been examining the following data sets:

SEND.CNTRITT and SEND.CNTRLES_ITT.

FDA STATISTICAL DISCUSSION POINTS FOR THE TELECONFERENCE

The following are statistical discussion points from the FDA statistical reviewer, Dr. Anthony Mucci, 10\13\09, for the teleconference, 10\15\09:

My main problems are:

(1): For the “lesion level” data, where the rows are lesions (**CENRLES_ITT**):

I reduced the data set to include only **Ta**, **T1**, and Benign lesions. Once I effected this reduction, I examined, for instance, the variable **TaT1_wb**, subject to the restriction that the variable **PRTYPE** registered as **Ta** or **T1**. In this context, **TaT1_wb** should register as = 1, since the lesion was confirmed as **Ta** or **T1** by histology, according to **PRTYPE**, and the specimen wouldn't have been available for histology if White Light and/or Blue Light didn't detect it. But, the variable **TaT1_wb** sometimes registers = 0 in this scenario, implying that neither diagnostic saw the lesion. How can this be?

FDA STATISTICAL DISCUSSION POINTS FOR THE TELECONFERENCE(cont.)

(2): Again, using the subset of **CENTRLES_ITT** consisting of Ta, T1 and benign lesions, I find:

Benign = 137 ; # Ta Lesions = 566 ; # T1 Lesions = 134.

In the submission, Section 7.4.1, Table 16, Photocure lists :

Ta Lesions = 580 ; # T1 Lesions = 95 (I can't find # Normals in the submission.)

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NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
10/13/2009

***CONFIDENTIAL**

FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com

Regarding NDA 22-555: Hexvix, submission dated June 30, 2009, the FDA would like to discuss the STATISTICAL data at the teleconference scheduled for:

Thursday, October 15, 2009, at 12:00 – 2:00 pm, US EST

***Provide a toll-free Dial-In # (with 8 lines), by 12:00 pm, EST, 10\14\09 (via email to my attention: Thuy Nguyen, Project Manager).**

If you have any questions, please feel free to contact me.

FDA STATISTICAL INFORMATION REQUEST

The following are FDA statistical comments, 10\13\09, from the statistical reviewer, Dr. Anthony Mucci, in preparation for the teleconference:

I am having difficulty verifying your statistical results; it is conceivable that I am not understanding the data sets. I need to talk with the stat and programming people with both sides in front of the respective computers so that we can go through the definitions and some calculations. I have been examining the following data sets:

SEND.CNTRITT and SEND.CNTRLES_ITT.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
10/13/2009

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FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, 2009, the FDA has the following PHARMACOLOGY\TOXICOLOGY Information Request – October 13, 2009.

By 9:00 am, EST, Friday, October 16, 2009, provide an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22-555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA PHARMACOLOGY\TOXICOLOGY INFORMATION REQUEST

Regarding NDA 22-555: Hexvix, submission dated June 30, 2009, the FDA has identified the following deficiencies in your reproductive and developmental toxicology studies (Study Nos: 494693, 494410, and 494431):

- No protocols included in all studies
- No toxicokinetics data
- No analysis of the formulations prepared at [REDACTED] (b) (4) with regard to stability, concentration and homogeneity
- Significant amounts of dosing errors

Submit the following data:

- The protocols for all reproductive and developmental toxicology studies
- Data regarding verification of stability, concentration and homogeneity of the formulations

Please note that without dose concentration verification data and toxicokinetics data, the FDA will be unable to evaluate the adequacy of drug exposure.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
10/13/2009

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FDA CDER - DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

**TO: Ms. Lynda Sutton (for Photocure ASA)
Cato Research
Office: (919) 361-2286
Email: LSutton@cato.com**

Regarding NDA 22-555: Hexvix, submission dated June 30, 2009, the FDA has the following CLINICAL Information Request – October 1, 2009.

By Tuesday, October 13, 2009, provide an official response to the NDA via Gateway / GSR electronic submission to the FDA, as with all submissions regarding NDA 22-555. Additional comments may be forthcoming.

If you have any questions, please feel free to contact me.

FDA CLINICAL INFORMATION REQUEST

In the Periodic Safety Update Report dated February 2009, included in NDA 22-555 (Hexvix), submission dated June 30, 2009, Section 5.3.6.2, are reports of two cases of azotemia associated with anuria from among four cases of off-label administration of Hexvix into the ureter in order to assist in the detection of urothelial ureteral carcinoma. In one case instillation was into one ureter and in the other case instillation was into both ureters.

- a) Provide the following additional information regarding these cases of intra-ureteral administration:
1. Are you aware of additional examples of instillation of Hexvix directly into the ureter? If so, what was the experience with these additional patients?
 2. Did this investigator instill Hexvix into the ureters of additional patients? If so, what was the experience following the intra-ureteral administration to the other two patients listed in the PSU report as well as in any additional patients?
 3. What is your explanation for the mechanism(s) responsible for this “azotemia” associated with ureteral instillation of Hexvix? Are you aware of any renal toxicity inducible by instillation of Hexvix directly into the kidney or absorbed via diseased tissues (inflammatory or malignant)?

FDA CLINICAL INFORMATION REQUEST (cont.)

4. Regarding these two cases of azotemia, provide the following missing information:
 - i. Were these cases of azotemia examples of anuria (zero urinary output) or oliguria (decreased urinary output)?
 - ii. Did the patient with only left ureteral instrumentation have two kidneys, or was the right one previously diseased or removed?
 - iii. Did these patients have ureteral obstruction or other pathological conditions that put the patients at risk for obstruction?
- b) Cases of impaired renal function, following Hexvix administration, have been observed in your Clinical Development Program.
 1. Identify all cases of impaired renal function (azotemia, creatinine elevation, BUN elevation and/or diminished urinary output), summarize each case including concomitant medications, co-morbidities, surgical complications, an approximation of severity, explanation of etiologic mechanisms (potential relationship to Hexvix administration) and outcomes.
 2. Summarize all cases identified in Tabular Format.
 3. Provide detailed Case Reports for all cases identified including the death attributed to azotemia observed in study B304/04.
- c) Comment briefly on what is known about the relationship, if any, between the circulating levels of aminolevulinic acid, or its derivatives such as hexylaminolevulinic acid, and the risks of nephrotoxicity, hepatotoxicity or other systemic adverse effects.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

THUY M NGUYEN
10/01/2009



NDA 22-555

FILING COMMUNICATION

Cato Research, Ltd.
Attention: Lynda Sutton, Chief Regulatory Officer
U.S. Agent for Photocure ASA
Westpark Corporate Center
4364 South Alston Avenue
Durham, NC 27713

Dear Ms. Sutton:

Please refer to your new drug application (NDA) dated June 30, 2009, received June 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Hexvix[®] (hexaminolevulinate), 85mg Solution for Intravesical Use.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is Priority. Therefore, the user fee goal date is December 30, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 7, 2009.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

However, we have the following information requests:

Pharmacology/Toxicology:

1. Please submit the historic control data for the following studies:

- (b) (4) Study No. 494410, Report No. 28189
Title: P-1206, Developmental Toxicity Study in Rats
- (b) (4) Study No. 494431, Report No. 27871
Title: P-1206, Developmental Toxicity Study in Rabbits

Labeling (Physician's Labeling Rule Format):

2. We note that there is no “**Warnings and Precautions**” section in either the Highlights or the Full Prescribing Information contents of your proposed labeling. Please verify that this omission is correct and intentional.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information within 30 days of receipt of this letter. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please contact Trinh Scott, Regulatory Project Manager, at Trinh.Scott@fda.hhs.gov or (301) 796-3311.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22555	----- ORIG-1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

RAFEL D RIEVES
09/11/2009

REQUEST FOR STUDY ENDPOINTS CONSULTATION

TO (Division/Office): Study Endpoints and Label Development Team (SEALD) CDER/OND-IO White Oak Bldg 22, Mail Drop 6411			FROM (Division/Office): DMIHP, c/o Trinh Scott, RPM, 301-796-3311	
DATE OF CONSULT REQUEST September 3, 2009	IND/NDA/BLA NO. NDA 22-555	SERIAL NO/SUPPL. NO. 000	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT June 30, 2009
NAME OF DRUG Hexvix (hexaminolevulinate)		NAME OF SPONSOR/APPLICANT Photocure ASA		CLASSIFICATION OF DRUG ultrasound
REQUESTED COMPLETION DATE October 30, 2009				
DRUG DEVELOPMENT PHASE (pre-IND/NDA/BLA; IND/BB-IND Phase I, II, III; NDA/BLA): PDUFA date (if associated with NDA/BLA): December 30, 2009 (Priority Review)				
MEETING DATES FOR SUBMISSION (IF APPLICABLE) Internal: _____ Sponsor: _____ MEETING TYPE (A, B, C): _____				
STUDY ENDPOINT REVIEW (PLEASE FILL IN THE APPROPRIATE INFORMATION) PROPOSED INDICATION: Diagnostic imaging agent indicated for photodynamic blue light cystoscopy performed with Karl Storz Photodynamic Diagnosis (PDD) system, as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder. INSTRUMENT(S) TO BE EVALUATED: eCTD submission located in EDR available the following link: \\cdsesub1\evsprod\NDA022555\0000 IS A COPY OF INSTRUMENT(S) TO BE REVIEWED INCLUDED IN THE SUBMISSION? IF NOT, PLEASE OBTAIN A COPY FROM THE SPONSOR/APPLICANT.				
CONSULT REVIEW REQUESTED (PLEASE FILL IN A BRIEF SUMMARY OF WHAT IS BEING REQUESTED; INCLUDE INFORMATION ON THE TYPE OF DOCUMENT BEING REVIEWED SUCH AS SPA, PEDIATRIC WR, PROTOCOL) DMIHP is now reviewing the NDA for Hexvix, and would like an evaluation of the labeling provided with the application. This is an eCTD submission located in EDR. The Division may also request attendance at relevant internal meetings. Thank you.				
SIGNATURE OF REQUESTER			METHOD OF DELIVERY (Check one) <input type="checkbox"/> INTEROFFICE MAIL <input type="checkbox"/> HAND -CARRIED <input type="checkbox"/> E-MAIL	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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/s/

TRINH N SCOTT
09/03/2009

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: CDRH
Division: Division of Reproductive, Abdominal & Rad Devices (DRARD)
Mail Code: HF_- HFZ-470
Consulting Reviewer Name: Mary Jo Cornelius
Building/Room #: WO66, room 0204
Phone #: 301-796-7001
Fax #:
Email Address: Mary.Cornelius@fda.hhs.gov
RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER
Division: Division of Medical Imaging and Hematology Products
Mail Code: HFD-160
Requesting Reviewer Name: Scheldon Kress
Building/Room #: WO 22, room 2179
Phone#: 301-796-1391
Fax #:
Email Address: Scheldon.Kress@fda.hhs.gov
RPM/CSO Name and Mail Code: Trinh Scott, HFD-160
Requesting Reviewer's Concurring Supervisor's Name: Rafel Rieves

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: August 19, 2009
Submission/Application Number: 22-555
Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product
Submission Receipt Date: June 30, 2009
Name of Product: Hexvix
Requested Completion Date: **October 30, 2009**
Submission Type: NDA
Official Submission Due Date: December 30, 2009
Name of Firm: Photocure ASA

Intended Use: Hexvix is a diagnostic imaging agent indicated for photodynamic blue light cystoscopy performed with Karl Storz Photodynamic Diagnosis (PDD) system, as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate): The sponsor submitted Hexvix (hexaminolevulinate), NDA 22-555, to be used in combination with the Karl Storz Photodynamic Diagnosis (PDD) system for the detection of superficial bladder cancer. CDRH has previously reviewed the PDD system submitted by Karl Storz Endoscopy-America on July 22, 2005 under PMA P050027.

(b) (4)

NDA 22-555 is in eCTD format can be accessed via this link: \\cdsesub1\evsprod\NDA022555\0000\ . Please contact Trinh Scott (301-796-3311) if you cannot access the eCTD.

Please evaluate the information provided in this NDA and provide comments and recommendations. Thank you for your assistance.

Documents to be returned to Requesting Reviewer? π Yes π No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review π Collaborative Review

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22555	----- ORIG 1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

TRINH N SCOTT
09/01/2009



NDA 22-555

PRIORITY REVIEW DESIGNATION

Photocure ASA
c/o Cato Research, Ltd.
Attention: Lynda Sutton, Chief Regulatory Officer, Cato Research, Ltd.
Westpark Corporate Center
4364 South Alston Avenue
Durham, NC 27713

Dear Ms. Sutton:

Please refer to your new drug application (NDA) dated June 30, 2009, received June 30, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Hexvix (hexaminolevulinate), 85mg Solution for Intravesical Use.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is December 30, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 7, 2009.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before September 12, 2009.

If you have any questions, please contact Trinh Scott, Regulatory Project Manager, at Trinh.Scott@fda.hhs.gov or (301) 796-3311.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

RAFEL D RIEVES
08/24/2009

For Consulting Center Use Only:

Date Received: _____

Assigned to: _____

Date Assigned: _____

Assigned by: _____

Completed date: _____

Reviewer Initials: _____

Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):

Center: OC
Division: Office of Combination Products

Mail Code: HF_- HFG-3
Consulting Reviewer Name: Patricia Love, M.D.
Building/Room #: CRAB, Room 200
Phone #: 301-427-1933
Fax #:
Email Address: Patricia.Love@fda.hhs.gov
RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER
Division: Division of Medical Imaging and Hematology Products
Mail Code: HFD-160
Requesting Reviewer Name: Scheldon Kress, M.D.
Building/Room #: WO 22, room 2179
Phone#: 301-796-1391
Fax #:
Email Address: Scheldon.Kress@fda.hhs.gov
RPM/CSO Name and Mail Code: Trinh Scott, HFD-160
Requesting Reviewer's Concurring Supervisor's Name: Rafael Rieves, M.D.

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: August 18, 2009
Submission/Application Number: 22-555
Type of Product: Drug-device combination Drug-biologic combination Device-biologic combination
 Drug-device-biologic combination Not a combination product
Submission Receipt Date: June 30, 2009
Name of Product: Hexvix
Requested Completion Date: **October 30, 2009**
Submission Type: NDA
Official Submission Due Date: December 30, 2009
Name of Firm: Photocure ASA

Intended Use: Hexvix is a diagnostic imaging agent indicated for photodynamic blue light cystoscopy performed with Karl Storz Photodynamic Diagnosis (PDD) system, as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate): The sponsor submitted Hexvix (hexaminolevulinate), NDA 22-555, to be used in combination with the Karl Storz Photodynamic Diagnosis (PDD) system for the detection of superficial bladder cancer. CDRH had previously reviewed the PDD system submitted by Karl Storz Endoscopy-America on July 22, 2005 under PMA P050027.

(b) (4)

NDA 22-555 is in eCTD format can be accessed via this link: \\cdsesub1\evsprod\NDA022555\0000\ . Please contact Trinh Scott (301-796-3311) if you cannot access the eCTD.

Please evaluate the information provided in this NDA and provide comments and recommendations. Thank you for your assistance.

Documents to be returned to Requesting Reviewer? π Yes π No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: Consultative Review π Collaborative Review

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22555	----- ORIG 1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

TRINH N SCOTT
08/18/2009

REQUEST FOR CONSULTATION

TO (Office/Division): **Microbiology Division**
Attention: James McVey, Sylvia Gantt

FROM (Name, Office/Division, and Phone Number of Requestor): **Division of Medical Imaging and Hematology Products (HFD-160)**
Trinh Scott, RPM, DMIHP, (301) 796-3311

DATE
August 17, 2009

IND NO.

NDA NO.
22-555

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
June 30, 2009

NAME OF DRUG
Hexvix
(hexaminolevulinate)

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
Ultrasound

DESIRED COMPLETION DATE
October 30, 2009

NAME OF FIRM: **Photocure ASA**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

The purpose of this consult is to request review of the validation of sterilization for NDA 22-555.

DMIHP is now reviewing NDA 22-555 for Hexvix (hexaminolevulinate), a diagnostic imaging agent indicated for photodynamic blue light cystoscopy, as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder.

This NDA has a Priority Review with a PDUFA Goal Date of December 30, 2009.

The DMIHP Medical Officer is Scheldon Kress (301-796-1391), CMC reviewer is Ravindra Kasliwal (301-796-1386), and the Regulatory Project Manager is Trinh Scott (301-796-3311).

Please note that this NDA is an eCTD submission, and the EDR link is \\cdsesub1\evsprod\NDA022555\0000\.

We would like your consult review to be finalized in DARRTS by October 30, 2009.
Thank you for your assistance, and please contact me if you have any questions.

SIGNATURE OF REQUESTOR

Trinh Scott, (301) 796-3311

METHOD OF DELIVERY (Check one)

DFS

EMAIL

MAIL

HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22555	----- ORIG 1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

TRINH N SCOTT
08/18/2009

REQUEST FOR CONSULTATION

TO (Office/Division): **PMHS, Maternal Health Team**
Attention: **Rosemary Addy**

FROM (Name, Office/Division, and Phone Number of Requestor): **Division of Medical Imaging and Hematology Products (HFD-160)**
Trinh Scott, RPM, DMIHP, (301) 796-3311

DATE August 13, 2009	IND NO.	NDA NO. 22-555	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT June 30, 2009
NAME OF DRUG Hexvix (hexaminolevulinate)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Ultrasound	DESIRED COMPLETION DATE October 30, 2009

NAME OF FIRM: **Photocure ASA**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|--|

II. BIOMETRICS

- | | |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

The purpose of this consult is to request review of the proposed label for NDA 22-555 as it relates to pregnancy and lactation.

DMIHP is now reviewing NDA 22-555 for Hexvix (hexaminolevulinate), a diagnostic imaging agent indicated for photodynamic blue light cystoscopy, as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder. The sponsor requests full waiver of pediatric studies (<\\cdsesub1\evsprod\NDA022555\0000\m1\us\1-9-1-req-for-waiver-of-pediatric-studies.pdf>).

This NDA has a Priority Review with a PDUFA Goal Date of December 30, 2009.

The DMIHP Medical Officer is Scheldon Kress (301-796-2050 x1391), and the Regulatory Project Manager is Trinh Scott (301-796-3311).

Please note that this NDA is an eCTD submission, and labeling information can be found in Module 1.

We would like your consult review to be finalized in DARRTS by October 30, 2009.

Thank you for your assistance, and please contact me if you have any questions.

SIGNATURE OF REQUESTOR Trinh Scott, (301) 796-3311	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

TRINH N SCOTT
08/18/2009

REQUEST FOR CONSULTATION

TO (Office/Division): **OSE/DRISK**
Attn: Catherine Carr, Mary Dempsey

FROM (Name, Office/Division, and Phone Number of Requestor): **Division of Medical Imaging and Hematology Products (HFD-160)**
Trinh Scott, RPM, DMIHP, (301) 796-3311

DATE
August 13, 2009

IND NO.

NDA NO.
22-555

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
June 30, 2009

NAME OF DRUG
Hexvix
(hexaminolevulinate)

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
Ultrasound

DESIRED COMPLETION DATE
October 30, 2009

NAME OF FIRM: **Photocure ASA**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

The purpose of this consult is to request review of the Risk Management for a new NDA 22-555 submitted on June 30, 2009 for Hexvix (hexaminolevulinate). This NDA has a Priority Review with a PDUFA Goal Date of December 30, 2009.

The DMIHP Medical Officer is Sheldon Kress (301-796-2050 x1391), and the Regulatory Project Manager is Trinh Scott (301-796-3311).

Please note that this NDA is an eCTD submission. The link to this application is at:
\\cdsesub1\evsprod\NDA022555\0000

The proposed review due date of November 30, 2009 is negotiable pending the overall review of this NDA. Thank you for your assistance, and feel free to call me if you have any questions.

SIGNATURE OF REQUESTOR Trinh Scott	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22555	----- ORIG 1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

TRINH N SCOTT
08/18/2009

REQUEST FOR CONSULTATION

TO (Office/Division): Director, Division of Medication Error and Prevention Analysis (DMEPA), HFD-420
Attn: Catherine Carr

FROM (Name, Office/Division, and Phone Number of Requestor): Division of Medical Imaging and Hematology Products (HFD-160)
Trinh Scott, RPM, DMIHP, (301) 796-3311

DATE
August 13, 2009

IND NO.

NDA NO.
22-555

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
June 30, 2009

NAME OF DRUG
Hexvix
(hexaminolevulinate)

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
Ultrasound

DESIRED COMPLETION DATE
October 30, 2009

NAME OF FIRM: Photocure ASA

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

The purpose of this consult is to request review of the proposed container labeling for a new NDA 22-555 submitted on June 30, 2009 for Hexvix (hexaminolevulinate).

This NDA has a Priority Review with a PDUFA Goal Date of December 30, 2009.

The DMIHP Medical Officer is Scheldon Kress (301-796-2050 x1391), and the Regulatory Project Manager is Trinh Scott (301-796-3311).

Please note that this NDA is an eCTD submission (\\cdsesub1\evsprod\NDA022555\0000), and labeling information can be found in Module 1.

We would like your consult review to be finalized in DARRTS by October 30, 2009.

Thank you for your assistance, and please contact me if you have any questions.

SIGNATURE OF REQUESTOR
Trinh Scott, (301) 796-3311

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22555	----- ORIG 1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

TRINH N SCOTT
08/18/2009

REQUEST FOR CONSULTATION

TO (Office/Division): **DDMAC**
Attention: Michelle Safarik, Paul Loebach

FROM (Name, Office/Division, and Phone Number of Requestor): **Division of Medical Imaging and Hematology Products (HFD-160)**
Trinh Scott, RPM, DMIHP, (301) 796-3311

DATE
August 13, 2009

IND NO.

NDA NO.
22-555

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
June 30, 2009

NAME OF DRUG
Hexvix
(hexaminolevulinate)

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
ultrasound

DESIRED COMPLETION DATE
October 30, 2009

NAME OF FIRM: **Photocure ASA**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

The purpose of this consult is to request review of the proposed labeling for a new NDA 22-555 submitted on June 30, 2009 for Hexvix (hexaminolevulinate). This NDA has a Priority Review with a PDUFA Goal Date of December 30, 2009.

The DMIHP Medical Officer is Sheldon Kress (301-796-1391), and the Regulatory Project Manager is Trinh Scott (301-796-3311).

This is an eCTD submission (\\cdsesub1\evsprod\NDA022555\0000), and the labeling information can be found in Module 1.

We would like your consult review to be finalized in DARRTS by October 30, 2009.

Thank you for your assistance, and feel free to call me if you have any questions.

SIGNATURE OF REQUESTOR Trinh Scott	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22555	----- ORIG 1	----- PHOTOCURE ASA	----- HEXVIX

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/s/

TRINH N SCOTT
08/18/2009

REQUEST FOR CONSULTATION

TO (Office/Division): **OND/ODEIII/Division of Reproductive and Urologic Products**
Attention: **Margaret Kober (for George Benson, MD)**

FROM (Name, Office/Division, and Phone Number of Requestor): **Division of Medical Imaging and Hematology Products (HFD-160), Trinh Scott, 301-796-3311**

DATE
July 22, 2009

IND NO.

NDA NO.
NDA 22-555

TYPE OF DOCUMENT
Original NDA

DATE OF DOCUMENT
June 30, 2009

NAME OF DRUG
Hexvix
(hexaminolevulinate)

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG
ultrasound

DESIRED COMPLETION DATE
August 10, 2009

NAME OF FIRM: **Photocure ASA (c/o Cato Research, Ltd.)**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This new NDA references (b) (4). The sponsor has requested Priority Review designation on the basis that Hexvix photodynamic blue light cystoscopy is an innovative product that significantly improves the detection of papillary bladder cancer compared to current methods.

The EDR link for this submission is: \\CDSESUB1\EVSPROD\NDA022555\0000

We request members of the review team for (b) (4) to assess the justification for NDA 22-555 and provide a recommendation for review designation. We would like the recommendation before our Filing Meeting of August 12, 2009.

The Medical Reviewer in DMIHP for this NDA is Sheldon Kress.

Thank you for your assistance; please feel free to call me with any questions.

SIGNATURE OF REQUESTOR Trinh Scott (301) 796-3311	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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this page is the manifestation of the electronic signature.**

/s/

Trinh Scott

7/22/2009 03:31:05 PM



NDA 22-555

Photocure ASA
c/o Cato Research, Ltd.
Attention: Lynda Sutton
Westpark Corporate Center
4364 South Alston Avenue
Durham, NC 27713

Dear Ms. Sutton:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, submission dated June 30, 2009, for Hexvix (85mg hexaminolevulinate).

This is an application orientation meeting for you to present your development status of Hexvix. Please provide an electronic copy of the slides 24 hours prior to the meeting so that handouts can be made (and submit as a formal submission to the NDA). Please structure your presentation for approximately 45 minutes, leaving 45 minutes for questions and discussion. Your presentation should summarize the data that you are relying on to support market approval.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings between FDA and Sponsors or Applicants (May 2009)*. The meeting is scheduled for:

Date: August 6, 2009
Time: 12:00 PM – 1:30 PM (Eastern Standard Time)
Location: FDA/CDER
White Oak Building 22, Room 1311
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDER participants: Richard Pazdur, M.D., Office Director
Glen Jones, Ph.D., Associate Office Director
Rafel Rieves, M.D., Division Director
Liberio Marzella, M.D., Acting Deputy Division Director
Alex Gorovets, M.D., Ph.D., Medical Team Leader
Sheldon Kress, M.D., Medical Reviewer
Jyoti Zalkikar, Ph.D., Statistics Team Leader
Anthony Mucci, Ph.D., Statistics Reviewer
Adebayo Lanionu, Ph.D., Pharmacology/Toxicology Team Leader
Yanli Ouyang, Ph.D., Pharmacology/Toxicology Reviewer
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader

Christy John, Ph.D., Clinical Pharmacology Reviewer
Sarah Pope, Ph.D., Chemistry Team Leader
Ravindra Kasliwal, Ph.D., Chemistry Reviewer
James McVey, Ph.D., Microbiology Team Leader
Bryan Riley, Ph.D., Microbiology Reviewer
Mary Jo Cornelius, RN, Center for Devices and Radiological Health
George Benson, MD, Division of Urological and Reproductive Health
Kaye Kang, Pharm.D., Chief, Project Management Staff
Martin Kaufman, Regulatory Health Project Manager
Thuy Nguyen, M.P.H, Regulatory Health Project Manager
Trinh Scott, MSCS, Regulatory Health Project Manager

Please email the names of your attendees to me by July 23, 2009 so that I can give the security staff time to prepare temporary badges in advance. Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Trinh Scott, at (301) 796-3311; the division secretary, (301) 796-2050.

If you have any questions, please contact me at Trinh.Scott@fda.hhs.gov or (301) 796-3311.

Sincerely,

{See appended electronic signature page}

CDR Trinh Scott, USPHS
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

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this page is the manifestation of the electronic signature.**

/s/

Trinh Scott
7/20/2009 12:13:32 PM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 22555 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Cysview Established/Proper Name: Hexaminolevulinate Hydrochloride Kit For Intravesical Solution Dosage Form: 100 mg hexaminolevulinate hydrochloride powder and a vial containing 50 mL DILUENT for Hexaminolevulinate Hydrochloride in polypropylene		Applicant: Photocure Agent for Applicant (if applicable): Cato Research
RPM: Thuy Nguyen, M.P.H.		Division: Medical Imaging Products
<p>NDA: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		
<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check box and explain:</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>		
❖ Actions <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>June 1, 2010</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input type="checkbox"/> None Complete Response - December 30, 2009
❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority</p> <p>Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch</p> <p><input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch</p> <p><input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E</p> <p style="margin-left: 40px;"><input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41)</p> <p style="margin-left: 40px;"><input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p style="margin-left: 40px;">Subpart I Subpart H</p> <p style="margin-left: 80px;"><input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR</p> <p><input type="checkbox"/> Submitted in response to a PMC</p> <p><input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p>	
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

Copy of this Action Package Checklist ³	May 28, 2010
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) APPROVAL - May 28, 2010
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	FDA - May 19, 2010
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	March 31, 2010
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

³ Fill in blanks with dates of reviews, letters, etc.:
Version: 5/14/10.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	May 20 & 25, 2010
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	May 5, 2010
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM May 18, 2010 <input checked="" type="checkbox"/> DMEPA May 5, 2010 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC April 8, 2010 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	May 20, 2010
<ul style="list-style-type: none"> ❖ 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>October 14, 2009</u> If PeRC review not necessary, explain: _____ • Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>) 	Included
<ul style="list-style-type: none"> ❖ Internal memoranda, telecons, etc. 	Included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
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Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	March 3, 2010
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None May 25, 2010
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	
• Clinical review(s) (<i>indicate date for each review</i>)	May 13, 2010
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Clinical Rev - May 13, 2010
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)		<input type="checkbox"/> None
Biostatistics		<input checked="" type="checkbox"/> None
❖ Statistical Division Director Review(s) (indicate date for each review)		<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> None
Statistical Review(s) (indicate date for each review)		<input type="checkbox"/> None
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)		<input type="checkbox"/> None May 12, 2010
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)		<input checked="" type="checkbox"/> None
Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)		<input type="checkbox"/> None May 17, 2010
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)		<input checked="" type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)		<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)		<input checked="" type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)		<input type="checkbox"/> None May 17, 2010
❖ Microbiology Reviews		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)		<input checked="" type="checkbox"/> None

Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input checked="" type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	May 17, 2010
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)	Date completed: May 19, 2010 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed