CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-119

CORRESPONDENCE

QLT PhotoTherapeutics Inc.

DUPLICATE

500 West 6th Avenue

May 28, 1999

Dr. Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD
USA 20852

Attn: Document Control Room

Subject: Presubmission of Section 5 (Pharmacology/Toxicology) for an Original New Drug Application 21-119 for VISUDYNE™ (verteporfin for injection) for use in photodynamic therapy for the treatment of age-related macular degeneration (AMD) in patients with predominantly classic subfoveal choroidal neovascularization (CNV)

Dear Dr. Chambers:

QLT PhotoTherapeutics Inc. will be submitting a multipart application for components of a combination product consisting of VISUDYNE™ (verteporfin for injection), a photoactive drug for use in photodynamic therapy (PDT) of age-related macular degeneration (AMD) patients, and specified lasers for use as light sources for the photoactivation of VISUDYNE.

The organization and content of this multipart submission will conform to FDA policies and procedures for combination products (drug and device) as described in 21 CFR 3.2(e)(3) and further addressed in the CDRH/CDER Intercenter Agreement (Effective Date – October 31, 1991).

PART I contains the New Drug Application (NDA) and is to be reviewed by CDER. PARTS II and III are Premarket Approval Applications (PMAs) to be reviewed by CDRH. This multipart submission will consist of the following parts:

PART I – New Drug Application for VISUDYNE™ (verteporfin for injection) NDA 21-119, including complete clinical data.

PART II – Premarket Approval Application for the Coherent Opal Photoactivator Laser Console and LaserLink Adapter.

PART III – Premarket Approval Application for the Zeiss VISULAS 690s laser and VISULINK PDTadapter.

This first Presubmission of PART I consists of the complete nonclinical pharmacology and toxicology section (Section 5) of the NDA. It is comprised of a review copy and an archival copy of 56 volumes plus a CD-ROM of Volume 1 only. An additional two desk copies of Volume 1 have

been forwarded directly to Lori Gorski, Consumer Safety Officer. This submission has been prepared and is being submitted in accordance with 21 CFR 314.

The applicant and contacts for these applications are:

Applicant:

QLT PhotoTherapeutics Inc.[a]
c/o Bogle and Gates
Two Union Square
601 Union Street
Seattle, WA
USA 98101-2346

[a] a US subsidiary of QLT PhotoTherapeutics Inc. (Vancouver, BC, Canada).

Direct Sponsor Contact:

Alexandra DJ Mancini, MSc
Vice President, Regulatory Affairs
QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC
Canada V5Z 4H5

tel: (604) 872-7881
fax: (604) 707-7373

The existence of this multipart submission and the data and other information that it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905, 21 USC 331(j), 5 USC 552, and other applicable laws is hereby claimed.

We would be pleased to discuss this application with you. Please contact us at the addresses given above.

Sincerely,

QLT PHOTOTHERAPEUTICS INC.

Alexandra Mancini

Alexandra DJ Mancini, MSc
Vice President, Regulatory Affairs

cc: Mr. Richard Felten, Senior Reviewer, ODE I, CDRH, FDA (cover letter only)
Jonathan Kahan, US Representative, Hogan & Hartson (cover letter only)

QLT PhotoTherapeutics Inc.

520 West 6th Ave
Vancouver BC
Canada V5Z 4H5
Telephone 604 872 7441
Fax 604 875 8921

August 14, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD
USA 20852

Attn: Document Control Room

Subject: Original Drug-Device Combination-Product Submission consisting of three parts (one New Drug Application and two Premarket Approval Applications) as described below

Dear Dr. Chambers:

QLT PhotoTherapeutics Inc. is submitting a multipart application for components of a combination product consisting of VISUDYNE™ (verteporfin for injection), a photoactive drug for use in photodynamic therapy (PDT) for the treatment of patients with age-related macular degeneration (AMD), and specified lasers for use as light sources for the photoactivation of VISUDYNE. The organization and content of this multipart submission are intended to conform to FDA policies and procedures for combination products (drug and device) as described in 21 CFR 3.2(e)(3) and further addressed in the CDRH/CDER Intercenter Agreement (Effective Date – October 31, 1991).

PART I contains the New Drug Application (NDA) and is to be reviewed by CDER. PARTS II and III are Premarket Approval Applications (PMAs) to be reviewed by CDRH. Each PART contains this cover letter, plus a separate cover letter specific for that PART. The multipart submission consists of the following.

PART I – New Drug Application for VISUDYNE™ (verteporfin for injection) NDA 21-119, including complete clinical data.

PART II – Premarket Approval Application for the Coherent Opal Photoactivator Laser Console and LaserLink Adapter.

PART III – Premarket Approval Application for the Zeiss VISULAS 690s laser and VISULINK PDT

The NDA is being submitted to CDER and the PMAs are being submitted to CDRH. An archive copy of the PMAs is being sent to CDER with the NDA.

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Fifteen deskcopies of the NDA Summary (Section 2) (Volume 1) and a single deskcopy of the Electronic Submission (Section 14) (Volumes 251 to 253) have been sent directly to Lori Gorski, Project Manager, DAAODP, CDER.

Copy 1 of Volume 1 to CDER contains a single copy of the two CD-ROMs for the NDA, which contain all wordprocessed documents and electronic data files for the NDA. The deskcopy of NDA Volume 1 to CDRH contains a single CD-ROM of the two PMAs.

The applicant, contacts, and US representative for these applications are:

Applicant:

QLT PhotoTherapeutics Inc.[a]
c/o Scott L. Gelband, Attorney
Perkins Coie LLP
1201 Third Avenue, 40th Floor
Seattle, WA 98101-3099

[a] a US subsidiary of QLT PhotoTherapeutics Inc. (Vancouver, BC, Canada).

US Representative:

Jonathan Kahan
Hogan & Hartson
555 Thirteenth St., N.W.
Washington, D.C. 20004-1109

Tel: (202) 637-5600
Fax: (202) 637-5910

Direct Sponsor Contacts:

David Mitchell, Manager, Regulatory Affairs
Alexandra Mancini, Vice President, Regulatory Affairs
QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC
Canada V5Z 4H5

Tel: (604) 872-7881
Fax: (604) 707-7373

The clinical studies included in this combination product submission were conducted by QLT PhotoTherapeutics Inc. and CibaVision under IND [redacted] in accordance with 21 CFR Parts 50, 56, and 312.

.../p3

The existence of this multipart submission and the data and other information that it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905, 21 USC 331(j), 5 USC 552, and other applicable laws is hereby claimed.

We would be pleased to discuss this application with you. Please contact us at the addresses given above.

Sincerely,

QLT PHOTOTHERAPEUTICS INC.

Alexandra Mancini

Alexandra DJ Mancini, MSc
Vice President, Regulatory Affairs

cc: Richard Felten, Senior Reviewer, ODE I, CDRH, FDA (cover letter only)
Jonathan Kahan, US Representative, Hogan & Hartson (cover letter only)

APPEARS THIS WAY
ON ORIGINAL

QLT PhotoTherapeutics Inc.

520 West 6th Ave.
Vancouver, B.C. V5Z 4H5
Canada
Telephone 604 872 7441
Fax 604 872 0115

August 14, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD
USA 20852

Attn: Document Control Room

Subject: Original New Drug Application 21-119 for VISUDYNE™ (verteporfin for injection) for use in photodynamic therapy for the treatment of age-related macular degeneration (AMD) in patients with predominantly classic subfoveal choroidal neovascularization (CNV)

This is PART I of a multipart submission.

Dear Dr. Chambers:

QLT PhotoTherapeutics Inc. hereby submits PART I of a multipart application for components of a combination product consisting of VISUDYNE™ (verteporfin for injection), a photoactive drug for use in photodynamic therapy (PDT) for the treatment of patients with age-related macular degeneration (AMD), and specified lasers for use as light sources for the photoactivation of VISUDYNE.

The organization and content of this multipart submission conforms to FDA policies and procedures for combination products (drug and device) as described in 21 CFR 3.2(e)(3) and further addressed in the CDRH/CDER Intercenter Agreement (Effective Date – October 31, 1991).

PART I contains the New Drug Application (NDA) and is to be reviewed by CDER. PARTS II and III are Premarket Approval Applications (PMAs) to be reviewed by CDRH. Complete copies of PARTS II and III are also submitted to CDER for archive purposes. PART I consists of the following.

PART I – New Drug Application for VISUDYNE™ (verteporfin for injection) NDA 21-119, including complete clinical data. Note that a 56-volume presubmission to PART I (NDA Section 5, Preclinical) was submitted to CDER on May 28, 1999.

Included here are 255 original volumes (Volumes 1-253 plus Volumes 119A and 192A). In addition to the normal number of review copies, Ms. Lori Gorski, Project Manager, will receive 15 deskcopies of the NDA Summary – Section 2 (Volume 1) and one deskcopy of the Electronic Submission – Section 14 (Volumes 251 to 253). As requested, Copy 1 of deskcopy Volume 1 will contain a single copy of two CD-ROMS that contain all electronic documents and data files for this NDA.

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We commit that field copies of the Chemistry, Manufacturing, and Controls section of the NDA have been sent directly to the International Technical Operations Branch and the Detroit District Office in accordance with 21 CFR 314.50(d)(1)(v).

The required user fee has been submitted, and the assigned User Fee ID Number is 3757.

The applicant, US representative, and contacts for these applications are:

Applicant:

QLT PhotoTherapeutics Inc.*
c/o Scott L. Gelband, Attorney
Perkins Coie LLP
1201 Third Avenue, 40th Floor
Seattle, WA 98101-3099

* a US subsidiary of QLT PhotoTherapeutics Inc. (Vancouver, BC, Canada).

US Representative:

Jonathan Kahan
Hogan & Hartson
555 Thirteenth St., N.W.
Washington, D.C. 20004-1109

Tel: (202) 637-5600
Fax: (202) 637-5910

Direct Sponsor Contacts:

David Mitchell, Manager, Regulatory Affairs
Caroline Stokl, Manager, Regulatory Affairs (for Chemistry and Microbiology)
Alexandra Mancini, Vice President, Regulatory Affairs
QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC
Canada V5Z 4H5

Tel: (604) 872-7881
Fax: (604) 707-7373

The clinical studies included in this NDA were conducted by QLT PhotoTherapeutics Inc. and CibaVision under IND [redacted] in accordance with 21 CFR Parts 50, 56, and 312. This NDA has been prepared and is being submitted in accordance with 21 CFR 314.

According to 21 CFR 314.108 (b)(2), the Sponsor hereby claims exclusivity for verteporfin, a new chemical entity, which has not previously been approved under Section 505(b) of the Act.

As previously discussed with the Agency and per the Drug Classification and Priority Review Policy, this drug application meets the definitions for Type 1A therapeutic classification, as a new molecular entity of important therapeutic gain. The majority of patients with neovascular AMD are not eligible for laser photocoagulation, the only approved therapy for AMD. Accordingly, the Sponsor hereby requests a priority review.

.../p3

The existence of this multipart submission and the data and other information that it contains are confidential, and the protection afforded to such confidential information by 18 USC 1905, 21 USC 331(j), 5 USC 552, and other applicable laws is hereby claimed.

We would be pleased to discuss this application with you. Please contact us at the addresses given above.

Sincerely,

QLT PHOTOTHERAPEUTICS INC.

Alexandra Mancini

Alexandra DJ Mancini, MSc
Vice President, Regulatory Affairs

cc: Richard Felten, Senior Reviewer, ODE I, CDRH, FDA (cover letter only)
Jonathan Kahan, US Representative, Hogan & Hartson (cover letter only)

APPEARS THIS WAY
ON ORIGINAL

QLT PhotoTherapeutics Inc. 520 West 6th Avenue Vancouver, BC Canada V5Z 4H5
t 604.872.7881 f 604.875.0001 www.qltinc.com

August 20, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850

Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Amendment to a Pending Application
Request for Waiver from Pediatric Studies

Dear Dr. Chambers:

We hereby request a waiver from the requirement to perform clinical investigations in pediatric populations due to the fact that macular degeneration occurs primarily in the elderly.

Please contact me directly with any questions you may have regarding this submission.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Manager, Regulatory Affairs

cc: (letter only)
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA
Jonathan Kahan, U.S. Representative, Hogan & Hartson

HFD-550/Gorsicki L.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-119

AUG 20 1999

QLT PhotoTherapeutics Inc.
Attention: David Mitchell
Manager Regulatory Affairs
c/o Jonathan S. Kahan
Hogan and Hartson
555 Thirteenth Street, NW
Washington, D.C. 20004-1109

Dear Mr. Mitchell:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Visudyne (verteporfin for injection)

Therapeutic Classification: Priority (P)

Date of Application: August 14, 1999

Date of Receipt: August 16, 1999

Our Reference Number: NDA 21-119

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 15, 1999, in accordance with 21 CFR 314.101(a).

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Attention: Division Document Room
9201 Corporate Boulevard
Rockville, Maryland 20850-3202

If you have any questions, contact Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

/S/ 8/20/99

Anthony Zeccola
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

QLT PhotoTherapeutics Inc. 520 West 6th Avenue Vancouver, BC Canada V5Z 4H5
t 604.872.7881
f 604.875.0001
www.qltinc.com

September 8, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850

Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Amendment to a Pending Application

Dear Dr. Chambers:

Alexandra Mancini, Vice President, Regulatory Affairs has resigned from QLT and Larry Mandt, Director, Ciba Vision, has assumed Alexandra's responsibilities at this time. Below is an amendment to the Direct Sponsor Contact information provided in both the Application cover letter and the NDA cover letter.

Application Cover Letter:

Direct Sponsor Contacts:
David Mitchell, Manager, Regulatory Affairs
~~Alexandra Mancini, Vice President, Regulatory Affairs~~
Larry Mandt, Director, Regulatory Affairs (CIBA Vision)
QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC
Canada V5Z 4H5

Tel: (604) 872-7881
Fax: (604) 707-7373

Direct Sponsor Contacts:
David Mitchell, Manager, Regulatory Affairs
Larry Mandt, Director, Regulatory Affairs (CIBA Vision)
QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC
Canada V5Z 4H5

Tel: (604) 872-7881
Fax: (604) 707-7373

.../p.2

NDA Cover Letter:

Direct Sponsor Contacts:
David Mitchell, Manager, Regulatory Affairs
Caroline Stokl, Manager, Regulatory Affairs (for Chemistry and Microbiology)
~~Alexandra Mancini, Vice President, Regulatory Affairs~~
Larry Mandt, Director, Regulatory Affairs (CIBA Vision)
QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC
Canada V5Z 4H5

Tel: (604) 872-7881
Fax: (604) 707-7373

Direct Sponsor Contacts:
David Mitchell, Manager, Regulatory Affairs
Caroline Stokl, Manager, Regulatory Affairs (for Chemistry and Microbiology)
Larry Mandt, Director, Regulatory Affairs (CIBA Vision)
QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC
Canada V5Z 4H5

Tel: (604) 872-7881
Fax: (604) 707-7373

Please contact me directly, or Larry Mandt (604-707-7287) in my absence, with any questions you may have regarding this submission.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Manager, Regulatory Affairs

cc: (letter only)
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA
Jonathan Kahan, U.S. Representative, Hogan & Hartson

NDA 21-119

QLT PhotoTherapeutics Inc.
Attention: David Mitchell, M.Sc.
Manager Regulatory Affairs
c/o Jonathan S. Kahan
Hogan and Hartson
555 Thirteenth Street, NW
Washington, D.C. 20004-1109

SEP 16 1999

Dear Mr. Mitchell:

Reference is made to your correspondence dated August 20, 1999, requesting a waiver of pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for Visudyne (verteporfin for injection) for the treatment of age-related macular degeneration for the pediatric population.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

If you have questions, please contact Joanne Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Sincerely,

/S/ 9/16/99

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC Canada V5Z 4H5
t 604.872.7881
f 604.875.0001
www.qltinc.com

DUPLICATE

September 23, 1999

ORIG AMENDMENT

BC

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD
USA 20852

Attn: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
CMC Amendment

Dear Dr. Chambers:

Attached is a Chemistry and Manufacturing amendment as well as the response to the Chemistry Reviewer questions which were faxed by Lori Gorski on September 15, 1999.

If you have any questions please do not hesitate to contact me at the number above.

Sincerely,

QLT PHOTOTHERAPEUTICS INC.

Caroline Stokl

Caroline Stokl, Ph.D.
Manager, Regulatory Affairs

cc: Jonathan Kahan, US Representative, Hogan & Hartson (letter only)
Lori Gorski, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date SEP 27 1999

From Richard P. Felten, Division of General and Restorative Devices. ODE, CDRH

Subject Consulting Review for Protocol Amendment to IND [redacted] submitted by QLT PhotoTherapeutics to Study the Effects of Verteporfin for Injection in the Treatment of CNV

To

Lori Gorski, Project Manager, Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products, ODE, CDER

I have completed my review of the September 7, 1999 Amendment and have a couple of comments concerning the device related material.

The major concern/issue is the lack of information or mention of the VISULINK [redacted] adapter in this document although it is part of the PMA. If Zeiss really intends to market the [redacted] then I would expect them to be using it in these studies. I have also gone back and looked at IND [redacted] their treatment IND, and this adapter is not mentioned in this document either. Zeiss has stated in the PMA that VISULINK [redacted] adapter is needed for use with certain slit lamps. Company has also used wording that the devices being used in these 2 IND's are the same as those for which the PMA is being submitted. If the VISULINK [redacted] is to be used in these IND's then information about it would need to be included in both IND submittals.

There seems to be some inconsistency regarding description of treatment spot sizes, or I just haven't read the information correctly. On page 033 of the Amendment, maximum lesion size is stated as 4500 micron with treatment size being 5500 microns. On page 035 the maximum size is given as 6200 microns. Finally in Appendix 4, Device Summary on page 126, the laser/adapter specifications are given as lesion diameter of 5400 microns with treatment diameter of 6400 microns. Think this needs to be consistent.

The only other issue is one I will also be raising with the PMA's. In many places in both device documents the term "zoom lens" is used to discuss changing treatment spot size. However, when the device descriptions for the adapters are read and the illustrations examined, there is no mention of a "zoom lens" or description of a "zoom lens adjustment feature". Both the Zeiss and Coherent adapters do show a feature identified as a spot size setting feature. If the spot size setting is the zoom feature then the wording should be consistent within the documents so you are not looking for a feature that appears not to be present.

I don't believe these issues actually affect the conduct of the study. I recommend that the amendment be accepted from a device point of view and that these comments not affect the status of IND [redacted] The lack of information on the VISULINK [redacted] does not affect use

[redacted]

of the other adapters for treating patients. However, company should be contacted and asked to address these issues.

/S/

cc:

[redacted]

HFD-550/Div Files
HFD-550/MO/Chambers

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

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

SEP 30 1999

Re: P990049
Coherent Opal Photoactivator Diode Laser and LaserLink Adapter
Filed: August 20, 1999

Dear Mr. Kahan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial review of your premarket approval application (PMA). We are pleased to inform you that we have made a threshold determination that the PMA is sufficiently complete to permit a substantive review and is, therefore, suitable for filing. The filing date is August 20, 1999, which is the date of CDRH receipt of the PMA.

This letter reflects the current progress of our administrative and limited scientific review of your application. Please be advised that the decision to file the PMA does not imply that either an in-depth evaluation of the safety and effectiveness of the device has been performed or a decision about the approvablility of the application has been made. Rather, it represents a decision by CDRH that the application is sufficiently complete to begin the substantive review process. Further review of your application may result in deficiencies which will be communicated to you.

Following receipt of a filing letter, an applicant is required by 21 CFR 814.20(e) to update its pending PMA 3 months after the filing date with new safety and effectiveness information learned about the device from ongoing or completed studies when the information may reasonably affect an evaluation of the safety or effectiveness of the device or may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling.

This updated reporting is limited to studies sponsored by the applicant or to which the applicant has reasonable access. The update report should be consistent with the data reporting provisions of the protocol. Please submit clinical updates in three copies as an amendment to the PMA and include the above PMA reference number assigned to the PMA.

The PMA cannot be approved until FDA has determined that the manufacturing facilities, methods and controls comply with the conditions set forth in your application and the applicable requirements of the Quality System Regulation (21 CFR Part 820). The document, Guidance For

Preparation of PMA Manufacturing Information, that you received earlier, is based on the original Good Manufacturing Practice (GMP) Regulation. That regulation was superseded by the Quality System Regulation, which became effective on June 1, 1997.

The guidance document is currently under revision to conform with the additional requirements for design control established by the Quality System Regulation. Until the new guidance is available, you are not required to describe the design controls used for the PMA device. During the PMA inspection, however, you may be asked to demonstrate that any design operations for the PMA device, conducted after June 1, 1997, are in compliance with the design control requirements of 21 CFR 820.30.

If you have not already done so, please notify CDRH as soon as possible in the form of an amendment to the PMA if there will be a delay in setting up your manufacturing facility for production of the device, and provide the expected date that the facility will be prepared for an FDA inspection. If you have any questions regarding the status of your Quality System inspection please contact the Office of Compliance at (301)-594-4695, or your District Office.

It is possible that device related issues could be discussed during the Dermatologic and Ophthalmologic Advisory Panel meeting which will be held to discuss the NDA in which your devices are described. You will be notified of the location and date of this meeting. Any additional information to be included in your PMA should be submitted in the form of a PMA amendment and be received by FDA at least 6 weeks in advance of the scheduled advisory panel meeting in order for FDA and the panel members to have adequate time to review the new information. Information received by CDRH less than 6 weeks in advance of a scheduled advisory panel meeting will not be considered or reviewed at the meeting and may delay consideration of your PMA until a subsequent advisory panel meeting.

All correspondence regarding this PMA should be submitted in six copies in the form of a PMA amendment. Please address all submissions to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions regarding this letter, please contact Mr. Richard P. Felten at (301) 594-1307.

Sincerely yours.

/S/

Celia M. Witten, Ph.D., M.D.
Director
Division of General and
Restorative Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

cc:
NDA 21-119
HFD-550/Div Files

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

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

SEP 30 1999

Re: P990048
Zeiss VISULAS 690s Diode Laser, VISULINK PDT
[redacted] Slit Lamp Adapters
Filed: August 16, 1999

Dear Mr. Kahan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial review of your premarket approval application (PMA). We are pleased to inform you that we have made a threshold determination that the PMA is sufficiently complete to permit a substantive review and is, therefore, suitable for filing. The filing date is August 16, 1999, which is the date of CDRH receipt of the PMA.

This letter reflects the current progress of our administrative and limited scientific review of your application. Please be advised that the decision to file the PMA does not imply that either an in-depth evaluation of the safety and effectiveness of the device has been performed or a decision about the approvablility of the application has been made. Rather, it represents a decision by CDRH that the application is sufficiently complete to begin the substantive review process. Further review of your application may result in deficiencies which will be communicated to you.

Following receipt of a filing letter, an applicant is required by 21 CFR 814.20(e) to update its pending PMA 3 months after the filing date with new safety and effectiveness information learned about the device from ongoing or completed studies when the information may reasonably affect an evaluation of the safety or effectiveness of the device or may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the draft labeling.

This updated reporting is limited to studies sponsored by the applicant or to which the applicant has reasonable access. The update report should be consistent with the data reporting provisions of the protocol. Please submit clinical updates in three copies as an amendment to the PMA and include the above PMA reference number assigned to the PMA.

The PMA cannot be approved until FDA has determined that the manufacturing facilities, methods and controls comply with the conditions set forth in your application and the applicable requirements of the Quality System Regulation (21 CFR Part 820). The document, Guidance For Preparation of PMA Manufacturing Information, that you received earlier, is based on the original Good Manufacturing Practice (GMP) Regulation. That regulation was superseded by the Quality System Regulation, which became effective on June 1, 1997.

The guidance document is currently under revision to conform with the additional requirements for design control established by the Quality System Regulation. Until the new guidance is available, you are not required to describe the design controls used for the PMA device. During the PMA inspection, however, you may be asked to demonstrate that any design operations for the PMA device, conducted after June 1, 1997, are in compliance with the design control requirements of 21 CFR 820.30.

If you have not already done so, please notify CDRH as soon as possible in the form of an amendment to the PMA if there will be a delay in setting up your manufacturing facility for production of the device, and provide the expected date that the facility will be prepared for an FDA inspection. If you have any questions regarding the status of your Quality System inspection please contact the Office of Compliance at (301)-594-4695, or your District Office.

It is possible that device related issues could be discussed during the Dermatologic and Ophthalmologic Advisory Panel meeting which will be held to discuss the NDA in which your devices are described. You will be notified of the location and date of this meeting. Any additional information to be included in your PMA should be submitted in the form of a PMA amendment and be received by FDA at least 6 weeks in advance of the scheduled advisory panel meeting in order for FDA and the panel members to have adequate time to review the new information. Information received by CDRH less than 6 weeks in advance of a scheduled advisory panel meeting will not be considered or reviewed at the meeting and may delay consideration of your PMA until a subsequent advisory panel meeting.

All correspondence regarding this PMA should be submitted in six copies in the form of a PMA amendment. Please address all submissions to:

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions regarding this letter, please contact Mr. Richard P. Felten at (301) 594-1307.

Sincerely yours.

/S/

Celia M. Witten, Ph.D., M.D.
Director
Division of General and
Restorative Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

cc:
NDA 21-119
HFD-550/Div Files

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

ORIG AMENDMENT

B2

QLT PhotoTherapeutics Inc. 520 West 6th Avenue Vancouver, BC Canada V5Z 4H5
t 604.872.7881
f 604.875.0001
www.qltinc.com

October 6, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Amendment to a Pending Application
Electronic Database

Dear Dr. Chambers:

This response is in reference to your query discussed in a teleconference on September 30, 1999 concerning the [redacted] electronic database relating to Study [redacted] Specifically, clarification was requested for the data column RECDTRT that defines whether or not study treatment was administered and which relates to the column INTERIM that specifies whether or not an interim visit occured.

The RECDTRT variable for an interim visit refers to whether study treatment was administered at the scheduled visit that immediately preceded the interim visit noted and not whether treatment was administered at the interim visit. No study treatments were administered at interim visits.

The next column to the right is TRTNUM. In cases where a study treatment was administered at the scheduled visit immediately preceding the interim visit, the row is populated with the study treatment number of that preceding scheduled visit. When no study treatment was administered at the preceding scheduled visit, the row is populated with a "0".

This complication arose as a result of merging two different datasets of interim visits and scheduled visits. If you want to define who received study treatment at each visit and the treatment number received, our analyst advises that the [redacted] dataset should be used. All of the tables or analyses generated for the NDA which used the variable RECDTRT took this variable from the dataset [redacted] and not from [redacted]

We hope that this answers your question. If there are additional queries on the electronic database please let us know.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Manager, Regulatory Affairs

cc: Richard Felten, Senior Reviewer, ODE I, CDRH, FDA
Jonathan Kahan, U.S. Representative, Hogan & Hartson

DUPLICATE

ORIG AMENDMENT

B2

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
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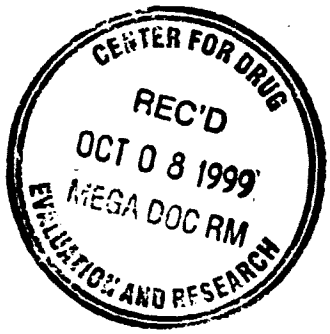
October 6, 1999



Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD
USA 20852

Attn: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Reviewer Questions

Dear Dr. Chambers:

Attached is additional Microbiology information, further to a telephone request from Dr. Carol Vincent.

If you have any questions please do not hesitate to contact me at the number above.

Sincerely,

QLT PHOTOTHERAPEUTICS INC.

Caroline Stokl

Caroline Stokl, Ph.D.
Manager, Regulatory Affairs

cc: Jonathan Kahan, US Representative, Hogan & Hartson (letter only)
Lori Gorski, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 1 2 1999

Ms. Alexandra DJ Mancini, MSc
Vice President, Regulatory Affairs
QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC Canada V5Z 4H5

Re: P990048 - Zeiss VISULAS 690s Laser and VISULINK PDT [redacted] Adaptor

Dear Ms. Mancini:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) is continuing to process the above named premarket approval application (PMA). Simultaneously with a review by the Office of Device Evaluation (ODE), the Office of Compliance (OC) must review the manufacturing information in your PMA to determine that it is sufficiently complete and appropriately organized to permit FDA to determine whether your firm (or your contract manufacturer) has the capability of manufacturing your PMA device in accordance with (1) the conditions specified in the PMA application and (2) the requirements of the medical device GMP regulation.

The Division of Enforcement II (DOE) of OC has reviewed the manufacturing section of your PMA and believes that it lacks the information necessary to effectively complete a review and determine whether to initiate a GMP inspection (see enclosed). While the deficiencies outlined in the enclosure do not preclude further review of your PMA, if left uncorrected they may delay or preclude evaluation of your manufacturing process and final approval of your PMA application. This letter is independent of correspondence you have received or will receive from ODE regarding the status of the review of the entire PMA. **Please be aware that a GMP inspection will not be scheduled until an adequate response to this deficiency letter is received by CDRH and your PMA is filed by ODE.** In addition, you should be aware that your response to the this deficiency letter does not affect the status of the ODE review (i.e., the filing decision).

We request that you respond as indicated. Please be advised that continued review by ODE of your application (including the manufacturing section) may identify additional deficiencies. Also, the OC review of your response to this letter may identify additional deficiencies.

For your information a Guidance for Preparation of PMA Manufacturing Information was published on March 22, 1991 (a notice of availability was published in the August 20, 1991 Federal Register). It is also available as part of the PMA Manual Supplement which may be obtained from the Division of Small Manufacturer's Assistance at 1-800-638-2041.

Information supplied in response to the enclosed request should be submitted in the form of an amendment AND BE CLEARLY IDENTIFIED AS A RESPONSE TO AN OC REQUEST IN YOUR REFERENCE BLOCK. FDA will consider the PMA to have been withdrawn voluntarily if you fail to respond in writing to this request for an amendment within 180 days of the date of this letter as provided under 21 CFR 814.44(g). You may, however, amend the PMA within the 180 day period to request an extension of time to respond. Any such request is subject to FDA approval and must justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180 day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180 day period will be considered a resubmission of the PMA and will be assigned a new number. A resubmission should be complete and self-contained without reference to earlier submissions because of potential difficulties in assembling files from storage.

All correspondence regarding this PMA should be submitted in three (3) copies in the form of a PMA amendment to the address below and reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
ATTN: Field Programs Branch, OC
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd., Room #120
Rockville, Maryland 20850

This letter reflects the current progress of our review of your application. Please be advised, however, that continued review of your application or questions arising from any response to this letter, may result in additional deficiencies being identified.

APPEARS THIS WAY
ON ORIGINAL

If you have any questions concerning this deficiency letter, please contact either Vertleen Covington at (301) 594-4695 or Allen T. Wynn at (301) 594-4695.

Sincerely yours,

/S/

Kathy Poneleit
Director
Premarket Approval
Application Program
Office of Device Evaluation
Center for Devices and
Radiological Health

APPEARS THIS WAY
ON ORIGINAL

DEFICIENCY LIST

The Office of Compliance (OC) in the Center for Devices and Radiological Health (CDRH) has completed an initial review of your original combined drug-device application part III, for the Zeiss VISULAS 690s laser and VISULINK PDT [redacted] adapters (P990048), dated August 15, 1999. Please address the following and provide the requested documentation, where applicable:

1. Verification/Validation protocols and documentation for the manufacturing processes for these devices.

2. Installation and Operational Qualification data for the most important pieces of manufacturing equipment used to manufacture these devices.

3. Documentation that employees have been trained to manufacture these devices.

4. Page 82 of volume 2 indicates that technical specialists from the units being audited may be called upon to take part in executing the audit. FDA does not consider this a good practice because these employees may introduce an element of bias towards the units being audited and lack impartiality.

5. Page 157 of volume 2 indicates that there is no limit to the archiving time for change documentation. However, it then goes on to say that destruction of change documentation requires prior consent from the R & D Manager. Under what conditions would this consent be given and these documents destroyed?

6. Page 167 of volume 2 indicates that original printouts and data carriers shall be retained for the minimum periods (at least 3 years) specified in the List of Document Evaluations and Retention Times. Then after the retention periods have elapsed, system or product-related quality documents may be transferred to the central archive. What is this minimum retention period based on? How long are the documents kept in the central archive? What is the expected lifetime of the devices?

7. Pages 46 and 67 of volume 3 contain copies of documents written in German. Please provide English translations of these documents.

8. Page 63 in volume 3 contains a document that is illegible because the boxes containing words cannot be read because of the shading (originals were in color?) present in the reviewer's copy of the document. Please provide a readable copy of this document.

9. Page 71 of volume 3 discusses your firm's MDR procedures. Please clarify whether reports of incidents that occur outside the U.S. for products that are also marketed in the U.S. are included in reports submitted by your U.S. subsidiaries.

cc:
NDA 21-119
HFD-550/Div Files

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 12 1999

Ms. Alexandra DJ Mancini, MSc
Vice President, Regulatory Affairs
QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC Canada V5Z 4H5

Re: P990049 - Coherent Opal Photoactivator Laser Console and LaserLink Adaptor

Dear Ms. Mancini:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) is continuing to process the above named premarket approval application (PMA). Simultaneously with a review by the Office of Device Evaluation (ODE), the Office of Compliance (OC) must review the manufacturing information in your PMA to determine that it is sufficiently complete and appropriately organized to permit FDA to determine whether your firm (or your contract manufacturer) has the capability of manufacturing your PMA device in accordance with (1) the conditions specified in the PMA application and (2) the requirements of the medical device GMP regulation.

The Division of Enforcement II (DOE) of OC has reviewed the manufacturing section of your PMA and believes that it lacks the information necessary to effectively complete a review and determine whether to initiate a GMP inspection (see enclosed). While the deficiencies outlined in the enclosure do not preclude further review of your PMA, if left uncorrected they may delay or preclude evaluation of your manufacturing process and final approval of your PMA application. This letter is independent of correspondence you have received or will receive from ODE regarding the status of the review of the entire PMA. **Please be aware that a GMP inspection will not be scheduled until an adequate response to this deficiency letter is received by CDRH and your PMA is filed by ODE.** In addition, you should be aware that your response to the this deficiency letter does not affect the status of the ODE review (i.e., the filing decision).

We request that you respond as indicated. Please be advised that continued review by ODE of your application (including the manufacturing section) may identify additional deficiencies. Also, the OC review of your response to this letter may identify additional deficiencies.

For your information a Guidance for Preparation of PMA Manufacturing Information was published on March 22, 1991 (a notice of availability was published in the August 20, 1991 Federal Register). It is also available as part of the PMA Manual Supplement which may be obtained from the Division of Small Manufacturer's Assistance at 1-800-638-2041.

Information supplied in response to the enclosed request should be submitted in the form of an amendment **AND BE CLEARLY IDENTIFIED AS A RESPONSE TO AN OC REQUEST IN YOUR REFERENCE BLOCK**. FDA will consider the PMA to have been withdrawn voluntarily if you fail to respond in writing to this request for an amendment within 180 days of the date of this letter as provided under 21 CFR 814.44(g). You may, however, amend the PMA within the 180 day period to request an extension of time to respond. Any such request is subject to FDA approval and must justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180 day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180 day period will be considered a resubmission of the PMA and will be assigned a new number. A resubmission should be complete and self-contained without reference to earlier submissions because of potential difficulties in assembling files from storage.

All correspondence regarding this PMA should be submitted in three (3) copies in the form of a PMA amendment to the address below and reference the above PMA number to expedite processing.

PMA Document Mail Center (HFZ-401)
ATTN: Field Programs Branch, OC
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd., Room #120
Rockville, Maryland 20850

This letter reflects the current progress of our review of your application. Please be advised, however, that continued review of your application or questions arising from any response to this letter, may result in additional deficiencies being identified.

APPEARS THIS WAY
ON ORIGINAL

If you have any questions concerning this deficiency letter, please contact either Vertleen Covington at (301) 594-4695 or Allen T. Wynn at (301) 594-4695.

Sincerely yours,

/S/

Kathy Poneleit
Director
Premarket Approval
Application Program
Office of Device Evaluation
Center for Devices and
Radiological Health

APPEARS THIS WAY
ON ORIGINAL

DEFICIENCY LIST

The Office of Compliance (OC) in the Center for Devices and Radiological Health (CDRH) has completed an initial review of your original combined drug-device application part II, for the Coherent Opal Photoactivator Laser Console and LaserLink Adapter (P990049), dated August 15, 1999. Please address the following and provide the requested documentation, where applicable:

1. On page 85 of volume 2, your application indicates that product performance and product reliability complaints should not be considered "safety complaints". These types of complaints could be malfunctions that could impact patient safety. Please provide your logic in not considering these to impact patient safety.

2. On pages 368-370 of volume 2, your firm provided documentation of some of its software validation test plan. Several items have the notation, "will test on next version". Why were they not tested on this version? Were they ever tested and where is the documentation to show this?

3. On pages 385-386 of volume 2, your firm provides a list of anomalies or design features noted during validation of the OPAL system that you state could result in user error and system misuse. However, there is a handwritten comment, "NOTE: None of the anomalies listed will cause any harm or injury to the patient." There is no explanation why you believe this. There is no proof to show that these features will not cause problems. You need to explain why you believe these features will not cause problems.

4. Pages 117-123 of volume 3, provide lists of employees and their training status for other laser models manufactured by your firm. Some of the training is listed as "C", certified, and some as "N", training not complete. I'm not sure what you are trying to show here. Have any employees been trained on the Coherent Opal Photactivator Laser Console? Does some of the training regarding other laser models relate to the Opal? If this is true, you need to specify which types of training are relevant to the Opal. Also, the meaning of "N" is not clear. When is the training expected to be complete?

5. Page 232 of volume 3 provides a flowchart for electrostatic discharge control. It indicates that employees are required to document testing wrist straps when used, but are not required to document testing of heel straps prior to entering the work area? Why the discrepancy?

6. Page 234 of volume 3 contains the Coherent Opal Photoactivator Installation Procedure. In it, the dimensions of the device are only listed as L, H and W and the weight as XX. Yet further in the application (i.e., Page 236), there are known measurements applied to these designations. Why were these omitted from the installation procedure?

7. Page 264 of volume 3 contains the Opal Label sheet. There are some hand-written comments that are not clear. Under the console labels, there is a note "Human Use only Side

of ?" and there is another note that says "CE Label Removed ?" What do these notes mean and why they are there?

8. Appendix 97 contains service statistics for other models of lasers manufactured by QLT. No statistics for the Opal Photoactivator Laser Console or LaserLink Adapter are included. I'm not sure why you included this information in this application. It doesn't seem relevant.

cc:
NDA 21-119
HFD-550/Div Files

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC Canada V5Z 4H5
t 604.872.7881
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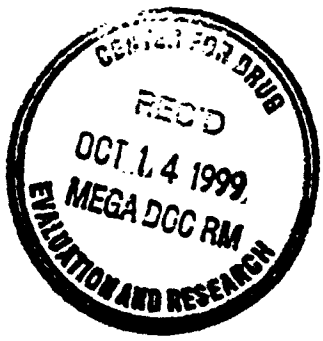
www.qltinc.com



October 12, 1999

ORIG AMENDMENT

BB

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

BEST POSSIBLE COPY

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Amendment to a Pending Application
Pharmacokinetics

Dear Dr. Chambers:

Enclosed please find the additional pharmacokinetic information requested by the Agency.

Biopharmaceutics Request

In Study BPD OCR 001, summary of mean plasma concentrations of verteporfin have been provided after 5 or 10-minute infusions. Could the sponsor provide a reanalysis of the data based on the five treatment regimens along with the light dose for each treatment level. Also provide 'N' for each treatment regimen and each light light dose within each treatment regimen. Also provide summary tables based on this reanalysis. For example, plasma concentrations for, Regimen 1, light dose 50J/cm2; Regimen 1, light dose 75K/cm2 etc.

Also provide tables of individual plasma concentrations of verteporfin at each time-point based on concentrations of the two regioisomers. These tables should be based on treatment regimens grouped together, with the sequential increase of light dose. Currently, Appendix E.3.1 provided the raw data in terms of the regioisomers only and the order seems to be arranged by sites. It will be easier to look at the raw data, if arranged according to the regimen and light dose grouped together.

Sponsor Response

Three summary tables are attached to address the first part of this request, one for each gender and one for all subjects combined. The order of presentation is similar to Tables 27 and 28 in Clinical Study Report BPD OCR 001.

.../p.2

The second part of the request is addressed by a Listing of Individual Plasma Concentrations. This listing is similar in presentation to Appendix E.3.1 of the Clinical Study Report BPD OCR 001, except that it is sorted according to the regimen and light dose. It also presents the verteporfin concentrations in addition to the two regioisomers separately.

Please contact me directly with any questions you may have regarding this amendment.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Manager, Regulatory Affairs

cc: (cover letter)
Richard Felten, Senior Reviewer, ODE I. CDRH, FDA
Jonathan Kahan, U.S. Representative, Hogan & Hartson

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC Canada V5Z 4H5
t 604.872.7881
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www.qltinc.com

ORIG AMENDMENT

BP

October 12, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

BEST POSSIBLE COPY

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Amendment to a Pending Application
Pharmacology/Toxicology

Dear Dr. Chambers:

Enclosed please find review and archival copies of our response to pharmacology/toxicology comments received from FDA on September 22, 1999.

Pharmacology/Toxicology Comment 1

Please clarify the following. Results from dogs identified as #101 and 151 appear in both References 121 [PH-93032; Cardiovascular Effects of Benzoporphyrin Derivative Monoacid Ring A (BPD-MA), a Photodynamic Therapy Agent, Without Photoactivation in the Beagle Dog], and 122 [PH-940014; Cardiovascular Effects of Benzoporphyrin Derivative Monoacid Ring A (BPD-MA), a Photodynamic Therapy Agent, Without Photoactivation in the Anesthetized Beagle Dog]. Please indicate if these are unique identifiers [e.g. does 101 and 151 refer to a specific animal] or are the same identifiers used for different studies. It was also noted that two animals [102 and 152] used in the study reported in Reference 121 were not euthanized but used in subsequent studies. Please indicate, if applicable to this submission, in which study they were used.

Sponsor Response 1

In reference 121 (PH-93032) and reference 122 (PH-94004), the numbers 101 and 151 are the animal numbers assigned at the start of each CTBR (ClinTrials BioResearch) study to a specific animal. For each study, the male numbers start at 101 and the female numbers start at 151. In addition, each animal has a unique permanent alphabetical tattoo as an identifier. Please refer to the accompanying memo from CTBR that follows this cover letter.

The two animals (102 and 152) referred to in reference 121 were not used in any other study reported in this submission.

.../p.2

Pharmacology/Toxicology Comment 2

In Study TX93-9003; Pilot Study: A Single Dose Intravenous Study in Dogs of Liposomal Benzoporphyrin Derivative Monoacid Ring A (BPD-MA; CL-318,952), it is indicated that female DA0113 had a sore on the scrotum. Please clarify this discrepancy.

Sponsor Response 2

In study TX-93003, the reference to a sore on the scrotum on female DA0113 is a coding error. The Coulston Foundation has been made aware of this discrepancy and will be issuing a final report amendment with a corrected Table 2. This correction is expected the week of October 11, 1999.

Please contact me directly with any questions you may have regarding this submission.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Manager, Regulatory Affairs

cc: (cover letter)
Richard Felten, Senior Reviewer, ODE I, CDRH, FDA
Jonathan Kahan, U.S. Representative, Hogan & Hartson

QLT PhotoTherapeutics Inc.
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October 14, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Amendment
Labeling
Production prints for vial and box

Dear Dr. Chambers:

Enclosed please find three copies of an amendment to the labeling information submitted in NDA 21-119: proposed final production prints for the VISUDYNE vial label and box. We would appreciate the Agency's review of these final drafts which are based on the draft vial and box labels on Pages 036-040 in Volume 1 of the August 14, 1999, NDA submission.

Please contact me directly with any questions you may have regarding this submission.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Manager, Regulatory Affairs

cc: Richard Felten, Senior Reviewer, ODE I, CDRH, FDA (cover letter)
Jonathan Kahan, U.S. Representative, Hogan & Hartson (cover letter)
Lori Gorski, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products (complete desk copy)

ORIGINAL

ORIG AMENDMENT

EC

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC Canada V5Z 4H5
t 604.872.7881
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www.qltinc.com

October 18, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD
USA 20852

Attn: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
CMC Amendment

Dear Dr. Chambers:

Attached is a Chemistry and Manufacturing amendment as well as the response to the Chemistry Reviewer questions which were faxed by Lori Gorski on October 12, 1999.

If you have any questions please do not hesitate to contact me at the number above.

Sincerely,

QLT PHOTOTHERAPEUTICS INC.

Caroline Stokl

Caroline Stokl, Ph.D.
Manager, Regulatory Affairs

cc: Jonathan Kahan, US Representative, Hogan & Hartson (letter only)
Lori Gorski, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products

ORIGINAL

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC Canada V5Z 4H5
t 604.872.7881
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www.qltinc.com

NEW CORRESP
NC

October 18, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Amendment
Advisory Committee Briefing Document

Dear Dr. Chambers:

Enclosed please find three copies of the briefing document for the November 17, 1999 Advisory Committee Meeting. An additional 12 desk copies have been sent directly to Lori Gorski, Project Manager, plus 20 copies for the advisory panel directly to Tracy Riley, Advisory Committee Coordinator.

Please contact me directly with any questions you may have regarding this submission.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Manager, Regulatory Affairs

cc: Richard Felten, Senior Reviewer, ODE I, CDRH, FDA (cover letter)
Jonathan Kahan, U.S. Representative, Hogan & Hartson (cover letter)
Lori Gorski, Project Manager, Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products, CDER (12 complete copies)

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC Canada V5Z 4H5
t 604.872.7881
f 604.875.0001
www.qltinc.com

October 26, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD
USA 20852

Attn: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Response to Reviewer Questions

Dear Dr. Chambers:

Attached is a response to a fax received on September 22, 1999 with questions from the Review Chemist.

If you have any questions please do not hesitate to contact me at the number above.

Sincerely,

QLT PHOTOTHERAPEUTICS INC.

Caroline Stokl

Caroline Stokl, Ph.D.
Manager, Regulatory Affairs

cc: Jonathan Kahan, US Representative, Hogan & Hartson (letter only)
Lori Gorski, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products
Allan Fenselau, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products (Desk Copy)

DUPLICATE

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC Canada V5Z 4H5
t 604.872.7881
f 604.875.0001
www.qltinc.com

November 1, 1999

ORIG AMENDMENT
BC

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD
USA 20852

Attn: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
CMC Amendment

Dear Dr. Chambers:

Attached is a copy of [redacted] Impurity Profiles of Intermediates and API manufactured from [redacted] This was requested by Allan Fenselau in a fax dated October 28th, 1999.

If you have any questions please do not hesitate to contact me at the number above.

Sincerely,

QLT PHOTOTHERAPEUTICS INC.

Caroline Stokl

Caroline Stokl, Ph.D.
Manager, Regulatory Affairs

cc: Jonathan Kahan, US Representative, Hogan & Hartson (letter only)
Lori Gorski, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products
Allan Fenselau, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products

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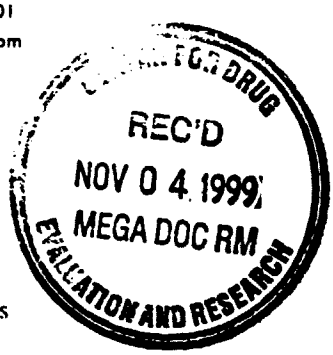
DUPLICATE

ORIG AMENDMENT

BC



November 3, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD
USA 20852

Attn: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
CMC Amendment

Dear Dr. Chambers:

Attached is a response to faxes received on October 29 and November 1, 1999 with questions from the Review Chemist.

If you have any questions please do not hesitate to contact me at the number above.

Sincerely,

QLT PHOTOTHERAPEUTICS INC.

Caroline Stokl

Caroline Stokl, Ph.D.
Manager, Regulatory Affairs

cc: Jonathan Kahan, US Representative, Hogan & Hartson (letter only)
Lori Gorski, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products
Allan Fenselau, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products (Desk Copy)

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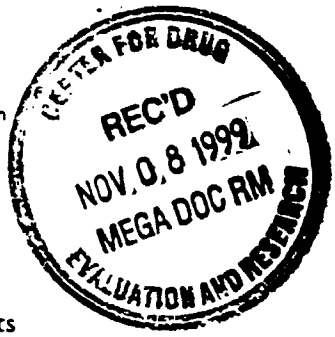

November 5, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
9201 Corporate Boulevard
Building 2
Rockville, Maryland
USA 20850
Attention: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
Amendment

Dear Dr. Chambers:

A "Modified FDA Format" New Drug Submission (NDS) for VISUDYNE was recently sent to Health Canada for review by the Bureau of Pharmaceutical Assessment (BPA). In that submission, we authorized the BPA to share information related to the review of the VISUDYNE NDS with the FDA. The name of Ms. Lori Gorski, Project Manager was provided as a point of contact with the FDA.

This amendment is to authorize FDA to share information in NDA 21-119 with the BPA.

The primary contact with the BPA concerning this product is:

Dr. Agnes V. Klein
Chief, Gastro-enterology Hematology Unit
Bureau of Pharmaceutical Assessment
Therapeutics Products Programme

Tel: (613) 941-0394
Fax: (613) 941-1365

Please contact me directly with any questions you may have regarding this submission.

Yours sincerely,

QLT PHOTOTHERAPEUTICS INC.

David Mitchell, M.Sc.
Senior Manager, Regulatory Affairs

cc: Richard Felten, Senior Reviewer, ODE I, CDRH, FDA
Jonathan Kahan, U.S. Representative, Hogan & Hartson

DUPLICATE

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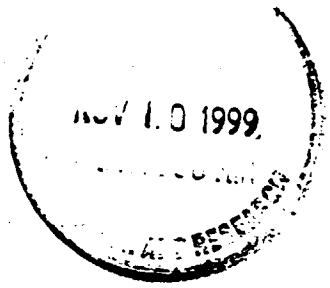
ORIG AMENDMENT
BC

November 9, 1999



Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD
USA 20852

Attn: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
CMC Amendment

Dear Dr. Chambers:

Attached is a response to faxes received on October 5, 13, 14, and 21, 1999 with questions from the Review Chemist.

If you have any questions please do not hesitate to contact me at the number above.

Sincerely,

QLT PHOTOTHERAPEUTICS INC.

Caroline Stokl

Caroline Stokl, Ph.D.
Manager, Regulatory Affairs

cc: Jonathan Kahan, US Representative, Hogan & Hartson (letter only)
Lori Gorski, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products
Allan Fenselau, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products (Desk Copy).

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, BC Canada V5Z 4H5
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November 10, 1999

Wiley Chambers, MD
Deputy Director
Division of Antiinflammatory, Analgesic and Ophthalmic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD
USA 20852

Attn: Document Control Room

NDA 21-119
VISUDYNE™ (verteporfin for injection)
CMC Amendment

Dear Dr. Chambers:

Attached is a response to faxes received on October 5, 13, 21, and November 5, 8, 10, 1999 with questions from the Review Chemist.

If you have any questions please do not hesitate to contact me at the number above.

Sincerely,

QLT PHOTOTHERAPEUTICS INC.

Caroline Stokl

Caroline Stokl, Ph.D.
Manager, Regulatory Affairs

cc: Jonathan Kahan, US Representative, Hogan & Hartson (letter only)
Lori Gorski, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products
Allan Fenselau, CDER Division of Analgesics, Anti-inflammatory and Ophthalmic Drug Products (Desk Copy)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

NOV 18 1999

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

Re: P990048
Zeiss VISULAS 690s Diode Laser and VISULINK PDT Slit Lamp Adapter
Filed: August 16, 1999
Amended: October 18 and November 2, 1999

Dear Mr. Kahan:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed an initial scientific review of your premarket approval application (PMA). We regret to inform you that on the basis of this review, we believe that the PMA lacks information needed by CDRH to effectively complete the review and determine whether there is reasonable assurance that the device is safe and effective for its intended use. While the deficiencies outlined below do not preclude further review of your PMA, if left uncorrected, they may ultimately preclude approval.

Our review noted the following deficiencies and, in order to correct these deficiencies we request the responses as indicated:

1. Following withdrawal of the [redacted] adapter, this application is now limited to the VISULAS 690s diode laser and the VISULINK PDT adapter. Both of these devices should be identified as part of the system Trade Name in the application.

2. Please clarify if the output wavelength of the laser is a single wavelength at [redacted] nm or is there a range of output, for example 689 +/- 3 nm. If the laser output is a range of wave lengths, then this notation should be used throughout the application.

3. In section 1.3.1, Device Description, line 4, a parenthetical statement "not part of the system described herein" follows a discussion of the adapters and the slit lamps to which they are attached. To what does this statement refer? Is this phrase intended to indicate that the slit lamps are not part of the application?

4 Since you have decided to withdraw the [redacted] from this application, does this mean that your system is no longer compatible with the [redacted] type slit lamp?

5 In the second paragraph of section 1.3.1, reference is made to VISULAS adapters. Are these the same as the VISULINK adapters previously mentioned in this section?

6. Please clarify the reference on page 32 to Figure 5, Items 1-3, in section 2.3.1, Laser. The Figure 5 located in section 2.2.2 has no numbers listed in the illustration and is not an illustration of an LCD screen with function keys. Figure 6 in section 2.3.1 appears to represent the LCD and laser control system with numbers 1-5.

7. Appendix 8.1 is the Operator Manual for the VISULAS 690s and the VISULINK PDT adapter. Figure 6 shows the VISULINK PDT while Figure 7 shows the completely assembled system. It is recommended that another illustration be provided showing the mating of these two systems with the corresponding numbering for attachment features.

8. In Appendix 8.1, Operation, there is a discussion of the zoom system and its' role in delivering the appropriate treatment energy. However, none of the illustrations of the VISULAS 690s and/or the VISULINK PDT adapter indicate a zoom adjustment or a zoom lens. Please clarify what is the zoom system and where on the VISULAS 690s or VISULINK PDT it is located.

9. Please certify whether or not your software is Y2K compatible.

This letter reflects the current progress of our review of your application. Please be advised that further substantive review of your application or any response to this letter may result in additional deficiencies.

As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. If you do not amend the PMA within the 180-day period to (1) correct the above deficiencies, or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number. Under these circumstances, any resubmission will be given a new PMA number and will be subject to the requirements of 21 CFR 814.20.

Information correcting the above deficiencies should be submitted in the form of an amendment. All correspondence regarding this PMA should be submitted in 3 copies in the form of a PMA amendment to the address below and reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this deficiency letter, please contact Mr. Richard P. Felten at (301) 594-1307.

Sincerely yours.

/S/

James E. Dillard III
Acting Director
Division of General and
Restorative Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

cc:
NDA 21-119
HFD-550/Div Files

APPEARS THIS WAY
ON ORIGINAL