

We remind you of the postmarketing study commitment you made in a letter dated November 19, 2003. The commitment is listed below:

1. To conduct a randomized, placebo-controlled study investigating the effects of Cialis® (tadalafil) tablets on color vision and retinal physiology (electroretinography) following multiple daily doses. The timeline is as follows:

Protocol Submission	within 3 months of the date of this letter
Study Initiation	within 10 months of the date of this letter
Final Report Submission	within 18 months of the date of this letter

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising,  
and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at [www.fda.gov/medwatch/report/mmp.htm](http://www.fda.gov/medwatch/report/mmp.htm).

If you have any questions, please call Eufrecina DeGuia, Regulatory Health Project Manager at (301) 827-4260.

Sincerely,

*{See appended electronic signature page}*

Florence Houn, M.D., M.P.H.  
Director  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosures:  
Physician Insert  
Patient Package Insert

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/s/

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Florence Houn

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-368

**FILE COPY**

Lilly ICOS LLC  
Attention: Catherine Melfi, Ph.D.  
U.S. Regulatory Affairs  
Lilly Research Laboratories  
Lilly Corporate Center  
Indianapolis, IN 46285

Dear Dr. Melfi:

Please refer to your new drug application dated June 28, 2001, received June 29, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cialis® (tadalafil), tablets 5mg, 10mg and 20mg.

We acknowledge receipt of your submissions dated June 28, July 24, August 27, September 10, 17, 18, and 25, October 1, 22, 25, and 30, November 5, and December 6, 2001; January 14 and 23, February 1, 6, 26, and 28, March 4, 6, 12, 18, 20, 22, and 25, April 1, 4, 5, and 16, May 10 (2), 14, 16, 24, and 30, June 6, 13, and 28, August 6, 8, 22, and 26, September 5, 12, 24, and 30, November 15 and 27, 2002, February 13, April 16 and 24, May 16, 27, and 30, June 5, 17, 24, and 26, July 15 and 22, August 7, 11, 19, and 29, September 11, October 9, 14, 15, 20 (2), and 24 (2), and November 5, 11, 12, 17, 19, and 20, 2003.

The May 27, 2003 submission constituted a complete response to our April 29, 2002 action letter.

This new drug application provides for the use of Cialis® (tadalafil) tablets for the treatment of erectile dysfunction.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 21-368." Approval of this submission by FDA is not required before the labeling is used.

NOV 21 2003

— STARRY

NDA 21-368

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Florence Houn, M.D., M.P.H.  
Director  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosures:  
Physician Insert  
Patient Package Insert

NOV 21 2003

E. BEARBY

## **H.2. Background/Overview of Clinical Investigations**

### ***H.2.1. Regulatory History and Agreements***

This section contains a summary of the significant FDA meetings, teleconferences, correspondence, and Investigational New Drug (IND) submissions that have occurred over the developmental history of IC351 (LY450190, tadalafil).

On 6 November 1997, ICOS Corporation submitted an Investigational New Drug (IND) application (IND 54,553) for IC351 to the Division of Reproductive and Urologic Drug Products (DRUDP) for the treatment of erectile dysfunction. The IND was received at FDA on 10 November 1997.

On 9 December 1997, IND 54,553 was placed on clinical hold due to preclinical safety concerns. Information needed to resolve the clinical hold was conveyed in a letter from FDA dated 16 December 1997. The information requested was as follows:

- Reports from the Glaxo 6-month rat and dog toxicity studies
- A 6-month oral toxicology study in monkeys was recommended to help determine if vasculitis is species-specific in dogs.
- Identification of biomarkers to monitor for vasculitis in men
- Enzyme kinetic data for phosphodiesterase (PDE) isozymes
- Multiple-dose pharmacokinetic data for target population
- Identification of the metabolite profile in men, including determination of whether major metabolites are biologically active.

In correspondence dated 5 February 1998, FDA sent comments on a proposed Phase 2 clinical protocol, which did not involve clinical hold issues. The correspondence also included recommendations for future Phase 3 protocols and some chemistry questions.

On 13 March 1998, ICOS Corporation submitted its response to the clinical hold. In a voicemail message received 24 March 1998, FDA indicated that the response to the clinical hold was not complete.

On 16 April 1998, summaries of nonclinical, clinical pharmacology, FDA contacts, and FDA discussions sent to Jim Morrison, Ombudsman for CDER, and on 24 April 1998, additional information was submitted to FDA in response to the clinical hold.

On 15 May 1998, draft interim pharmacokinetics report (LVBH [DSD02]) was submitted to FDA in response to the clinical hold. Agreement was reached in a face-to-face meeting between ICOS and FDA personnel on 26 May 1998 to proceed with human clinical trials prior to additional preclinical data submitted to the IND.

On 26 June 1998, a protocol synopsis for a proposed Phase 2 study (LVBF [DSD06]) was submitted to FDA for comment. Final protocol LVBF was submitted to FDA on 3 July 1998.

In correspondence from FDA dated 20 July 1998, additional pharmacology review comments that were not clinical hold issues were conveyed. These comments were as follows:

- Safety pharmacology studies were recommended to assess the effects of IC351 on gastrointestinal motility and gastric acid secretions
- Request to repeat the mouse lymphoma mammalian cell mutation assay using higher dose levels
- Results of in vivo genotoxicity assay need to be provided prior to Phase 2 clinical trials.

In a teleconference with FDA on 27 July 1998, ICOS agreed to amend protocol LVBF to monitor patients' erythrocyte sedimentation rate ([ESR] biomarker for vasculitis). The amended protocol LVBF was submitted to FDA on 27 July 1998. The clinical hold was lifted on 29 July 1998, and it was requested that the study report for LVBF be submitted prior to proceeding with additional U.S. clinical trials.

On 9 February 1999, IND 54,553 was transferred to Lilly ICOS LLC. The final study report for LVBF was submitted to the IND on 9 March 1999, and on 26 April 1999, Lilly ICOS requested the review of two Phase 3 protocols, LVBM and LVBK.

On 10 May 1999, Lilly ICOS submitted a request for a Carcinogenicity Assessment Committee (CAC) review for approval of the proposed doses for the oncogenicity studies in rats and mice.

In a teleconference between DRUDP and Lilly ICOS on 9 June 1999, the following agreements were reached regarding Phase 3 protocols:

- 20 mg IC351 is an acceptable dose from a safety perspective
- Primary endpoints should be the International Index of Erectile Function (IIEF) Erectile Function Domain and Sexual Encounter Profile (SEP) patient diary Question 2 and Question 3
- Exclusion criteria for cardiac arrhythmias should be revised so that patients with benign arrhythmias can be included in trials
- Active treatment duration was increased to 12 weeks
- Specific analysis of QTc interval was not planned, but a consult with Division of Cardio-renal will occur when a protocol is submitted
- Any secondary endpoints need to be adjusted for multiple comparisons and need to be derived from validated instruments to be considered to support the label

- Ophthalmology studies will be consulted to Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
- Use of short-acting nitrates by patients in trials will be considered pending review of the nitrate clinical drug interaction study data.

The dose selections for the 2-year rat and mouse carcinogenicity studies were acceptable, as conveyed in CAC meeting minutes dated 15 June 1999. In addition, circumstances were outlined for additional histopathology in the studies. In a teleconference on 23 June 1999, Dr. El Hage of FDA agreed that a gastric acid secretion study is not needed.

An IND animal safety report was submitted to FDA on 21 July 1999 that described compound-related testicular alterations in the 6-month chronic toxicity study in beagle dogs.

On 30 July 1999, a briefing document was submitted for a requested End of Phase 2 (EOP2) meeting.

In Chemistry, Manufacturing and Control (CM&C) meeting minutes dated 6 August 1999 the following agreements were outlined:

- The proposed starting materials are acceptable;
- The following should be provided in the New Drug Application (NDA): justification for variances from International Conference on Harmonisation (ICH) guidelines in the stability program; representative impurity profile chromatograms for the active pharmaceutical ingredient (API); justification for variances from ICH guidelines in residual solvent limits; the data, a database summary, and justification for the use of 0.5% sodium lauryl sulfate (SLS) in the dissolution test; and chiral inversion data;
- A specification for methylamine is not needed provided Lilly ICOS can provide proof that the methylamine is totally eliminated during the manufacturing process;
- Particle size and surface area need to be included in the specifications if they are important to the process control;
- A single-point specification at the timepoints proposed for the dissolution test are acceptable;
- Matrixing across strengths packaged in bottles is acceptable in principal. It was agreed that Lilly ICOS would choose a matrix design for drug product stability and will submit the data for statistical review prior to NDA submission.

At the EOP2 meeting on 30 August 1999, the following agreements were reached:

- Phase 3 trial comments – the proposed approach regarding dose selection is acceptable; the SEP is not considered validated but the revisions are acceptable; and patients on short-acting nitrates will be excluded
- One-year exposure for safety needs to be at exposures equivalent or above the marketed doses
- The proposal for financial disclosure information is acceptable
- Waiver for pediatric studies should be requested in NDA. In addition, Lilly ICOS agreed to propose a safety study to address the seminiferous tubule damage issue and to submit the full protocol of study LVBY (nitrates) for review.

Visual study protocol LVAN was discussed in a teleconference between Lilly ICOS and FDA on 8 September 1999.

On 4 October 1999, Lilly ICOS submitted a protocol outline for the sperm assessment study LVCD.

On 29 October 1999, FDA indicated that a 1-year dog toxicity study is needed to support safe clinical dosing beyond a 6-month duration. This was in response to the submission of the second 6-month dog toxicity study on 12 August 1999.

Draft protocol LVCC (visual study) was submitted for review on 3 November 1999.

On 5 November 1999, FDA provided interim guidance on the sperm assessment safety trial. Specifically, FDA indicated that semen assessment should be performed at Week 13 as well as Week 26, a Data Monitoring Board (DMB) should review these results to determine if Phase 3 trials can be initiated, and criteria to initiate Phase 3 trials should be provided to DRUDP in advance of their initiation. Additionally, FDA requested that patients with mild ED, with mild-moderate ED, and normal (no ED) subjects at least 45 years old should be included in these trials. FDA also indicated that the proposed endpoint using a mean analysis of sperm count is not appropriate, so a teleconference was scheduled for 2 December 1999 to reach agreement on the endpoint for this study.

An IND animal safety report was submitted to FDA on 24 November 1999 stating that neutropenia, thrombocytopenia, and/or decrease in hematocrit was observed in one mid-dose and one high-dose female in the 12-month dog study.

A teleconference to discuss the sperm assessment study was held on 2 December 1999. The endpoint agreed upon was proportion of subjects with reduction in sperm concentration of greater than or equal to 50% from baseline. Also, monthly complete blood count (CBC) monitoring was recommended based on the 24 November 1999 safety report, and DRUDP agreed to discuss the clinical relevance of results. Finally, FDA indicated that Phase 3 trials could not be initiated until after the DMB assessment of the Week 13 samples, although an adverse result in the trial will not necessarily signal an end

to clinical development of IC351. Sperm assessment protocol LVCD was submitted to FDA on 17 December 1999.

Comments from FDA on visual study protocol LVCC were received on 4 January 2000. On 4 February 2000, Lilly ICOS submitted a request for review of Cialis™ as the proposed trademark for IC351.

In correspondence dated 17 February 2000 regarding sperm assessment protocol LVCD, the FDA requested information regarding the exact statistical methodology to be used to answer the specific question asked in this study, and the FDA accepted the proposed independent DMB guidelines for the interim safety data assessment. The statistical methodology to be used in protocol LVCD was submitted to FDA on 6 March 2000.

On 15 March 2000, Lilly ICOS submitted additional information, requested by DRUDP, needed to complete preliminary review of the Cialis™ trademark.

Amended protocol LVCD was submitted to FDA on 3 April 2000.

A briefing document describing the proposed nitrate interaction package was submitted to FDA on 9 May 2000. On 16 June 2000 in a teleconference with the FDA Project Manager, a proposal was made to expand the requested nitrate interaction meeting to include a discussion of the clinical plan for the 20-mg IC351 dose. On 30 June 2000 an additional briefing document for the 3 August 2000 meeting was submitted that supplemented the 9 May 2000 briefing document by summarizing the proposed changes to the clinical registration plan for 20 mg IC351.

An IND animal safety report was submitted to FDA on 25 July 2000 that described compound-related testicular alterations in the 1-year chronic toxicity study in beagle dogs.

The following comments and agreements resulted from the 3 August 2000 meeting between Lilly ICOS and FDA:

- Division of Cardio-renal recommended that a) nitrate safety studies include higher IC351 doses (eg, 80 mg) to provide information on adequate margin of safety, and b) a positive control group be used in nitrate safety studies
- The proposed analysis plan for nitrate interaction studies is acceptable
- If pharmacology studies had demonstrated no interaction between IC351 and nitrates, use of nitrates in Phase 3 could be allowed
- The 3-month assessment showing noninferiority to placebo in sperm assessment study (LVCD) 10 mg IC351 is acceptable to support Phase 3 studies at 20 mg IC351

- There were concerns regarding sample size for the addition of a 20-mg IC351 treatment group to the existing study LVCD and regarding pooling placebo groups
- Semen assessment is not needed in open-label study LVBL since results will be obtained using 20 mg IC351 in LVCD using daily dosing
- Agreement on the adequacy of the proposed registration plan to support 20 mg IC351 could not be reached pending agreement on the design of the 20-mg IC351 sperm assessment study
- Lilly ICOS stated that exposures at 6 months and 1 year for 20 mg IC351 will meet ICH guidelines
- Drug-drug interaction studies at 20 mg IC351 using a CYP 3A4 substrate are acceptable; adequacy of studies using 10 mg IC351 with CYP 2C9 and CYP 1A2 will be a review issue
- Extrapolation of pharmacokinetic data from studies conducted with 10 mg to 20 mg IC351 will also be a review (labeling) issue
- Results of pharmacodynamic interaction studies with the 10-mg IC351 dose may not be extrapolated to the 20-mg IC351 dose.
- Lilly ICOS agreed to provide a fully revised version of protocol LVCD to assess 20-mg IC351 sperm effects.

In a teleconference on 11 August 2000, FDA indicated that the proposed analysis plan to add a 20-mg IC351 treatment group to sperm assessment study LVCD and to pool the control group is not acceptable. DRUDP did agree with a reduction in the semen volume criteria for that study to 1.5 mL. Lilly ICOS agreed to provide a protocol for a 20-mg IC351 sperm assessment study. On 8 September 2000, Lilly ICOS submitted 20-mg IC351 sperm assessment protocol LVCZ.

On 29 September 2000, Lilly ICOS sent FDA a DMB report for study LVCD stating that 10 mg IC351 was similar to placebo with respect to sperm effects (3-month results). On 13 October 2000, Lilly ICOS submitted to FDA a briefing document for a pre-NDA CM&C meeting.

In a telephone call on 23 October 2000, FDA Project Manager indicated that preliminary review by the Office of Postmarketing Drug Risk Assessment (OPDRA) of the trademark Cialis™ resulted in OPDRA recommending against the use of Cialis™ as a trademark. DRUDP, however, had not made a preliminary recommendation for or against the name Cialis™ at that time.

The following comment and agreements resulted from the 14 November 2000 pre-NDA CM&C meeting:

- The plan to include desiccant in drug substance packaging was acceptable

- The plan by Lilly ICOS to utilize four primary stability batches to satisfy the batch record requirement was accepted
- The proposal by Lilly ICOS to submit the NDA with 6 months of primary stability data for the 20-mg IC351 tablet and provide 12-month data during the review period was accepted.

On 13 December 2000, Lilly ICOS submitted a request to DRUDP for additional information on the OPDRA review of the trademark Cialis™. On 20 December 2000, Lilly ICOS submitted a request for a pre-NDA meeting.

The following agreements and comments were made at the pre-NDA meeting on 21 February 2001:

- The proposed formats and plans (proposed table of contents, Phase 3 study reports, representative selection of proposed tables and statistical analysis plan) are acceptable for the Phase 3 study reports
- A 3-month analysis report for study LVCQ is adequate to demonstrate efficacy; the integrity of the 6-month data is unknown due to the unblinding at 3 months, therefore the applicability of the 6-month data will be a review issue; an "alpha spend" will not apply. If the final 6-month study report is submitted at or before the 4-month safety update, it will not constitute a major amendment
- The proposed statistical analysis plan for the Integrated Summary of Effectiveness (ISE) is acceptable. FDA requested that conclusions on the explored data in the final dose response decision analysis be submitted in the NDA including dose response information, corrected analysis, and analysis leading to the final recommended dose. FDA requested that the tables that present Last Observation Carried Forward (LOCF) data should include the observed values, presented in a parallel analysis; if study centers are aggregated, a column should be included that identifies the study center in the data set. Also, given that the Phase 3 studies are conducted outside the US, FDA requested that Lilly ICOS provide in the ISE comments on interpretation of cross cultural differences, validation of the efficacy measures, and how data may be applied to the US population.
- The submission of the 6-month study results from study LVCZ will not be a major amendment if submitted at or before the 4-month safety update
- It is acceptable to use exposure data for the coprecipitate formulation of higher doses in support of meeting ICH exposure requirements for the proposed dose of the market image formulation; it could be a filing issue if ICH exposure requirements are not met at the time of submission

- The proposed statistical analysis plan for the Integrated Summary of Safety (ISS) is acceptable; the Division requests that a special safety section be provided in the ISS to include specific adverse events particularly the incidence and severity of back pain, eye disorders, effect on blood pressure, and cardiovascular and cerebrovascular adverse events; duration of adverse events as it relates to duration of exposure should be included in the safety analysis; sponsor should discuss and present benefit/risk ratio in the NDA
- The number and types of studies as proposed appears to be acceptable to support filing of the NDA
- It is acceptable to provide references in electronic format only
- The plans for the proposed electronic format is acceptable, the guidance document for industry regarding electronic submissions should be followed; a PROC CONTENTS (Statistical Application Software®[SAS] application) format for major efficacy files for the studies should be provided
- The approach to financial disclosure reporting information is acceptable. FDA requested that Lilly ICOS provide a table for each study listing the investigators, status of disclosure, and number of patients, as well as a description of the “due diligence” used to obtain information
- The rationale for a pediatric waiver appears to be acceptable, final determination will be made upon receipt of the waiver request
- The Clinical Pharmacology Biopharmaceutics Division requested that in vitro interaction studies which provide isoenzyme information 2C19 be included in the submission.
- Time to onset and duration of responsiveness will be a review issue; Lilly ICOS may request a teleconference to discuss this further
- The Division does not anticipate an Advisory Committee Meeting for this NDA.

On 26 March 2001, NDA and User Fee ID numbers were assigned to Lilly ICOS for this submission.

On 4 April 2001, Lilly ICOS submitted additional information to address specific concerns raised by OPDRA in their review of the trademark Cialis™. This information included an analysis of the name pairs Cialis™ versus Aralen® and Cialis™ versus Claritin®, along with additional information regarding an independent analysis of the name Cialis™ designed to assess the possibility of name confusion in written prescriptions.

On 5 April 2001, Lilly ICOS submitted a request for a teleconference to discuss the information to support label claims regarding the time to onset and period of

responsiveness of IC351 per Dr. Mark Hirsch's suggestion at the 21 February 2001 pre-NDA meeting. On 3 May 2001, DRUDP sent correspondence indicating that this request for a teleconference was denied, and that the issues would be considered with the NDA review.

On 18 April 2001, Lilly ICOS submitted an information amendment to IND 54,553 to update DRUDP on four clinical trial deaths that occurred since the one death reported in the previous IND annual report (10 August 2000). None of the deaths were assessed by investigators or sponsor to be related to study drug or protocol procedures.

On 29 June 2001, Lilly ICOS submitted a New Drug Application (NDA 21-368) for (Cialis (tadalafil)).

On 13 July 2001, FDA sent acknowledgement letter on acceptance of NDA 21-368. The primary user fee goal date is 29 April 2002.

On 24 July 2001, Lilly ICOS requested a Type B meeting to obtain a brief status report from DRUDP on the NDA review and for Lilly ICOS to provide a brief update on the LVCZ (20 mg sperm assessment) and LVCQ (6-month Phase 3 study) studies.

On 13 August 2001, Lilly ICOS provided information regarding the derivation of the primary efficacy variables for Study LVDG (duration of responsiveness) and details on the repeated measures analysis conducted for LVDG and LVCK (time to responsiveness)

On 29 August 2001, FDA accepted Lilly ICOS's proposal for the content and format of the 4-month safety update.

On 17 September 2001, Lilly ICOS submitted study reports LVCZ (20 mg sperm assessment) and LVCQ (6-month Phase 3 study) to the NDA as discussed and agreed upon at the pre-NDA meeting.

On 18 September 2001, Lilly ICOS submitted documentation regarding the adoption of the generic name tadalafil by the USAN.

On 20 August 2001, Lilly ICOS met with FDA to discuss a proposal to conduct an ED study over the Internet. The sponsor agreed to submit additional information prior to the start of the study.

On 25 September 2001, Lilly ICOS submitted revised container labels.

On 22 October 2001, Lilly ICOS submitted a sample of the to-be-marketed 20 mg tablet per an FDA request.

On 25 October 2001, Lilly ICOS submitted the 4-Month Safety Update.

In a teleconference on 14 December 2001, the DRUDP project manager provided an update of the NDA review to Lilly ICOS. The FDA reviewers had met for the 6-month status meeting for NDA 21-368. Reviews are on track for a 10-month review. There was one information request for the NDA location(s) of information on QT assessment. The requested information was submitted on 14 January 2002.

In a teleconference on 14 January 2002, the DRUDP project manager provided an update of the NDA review to Lilly ICOS. OPDRA issued a "no objection" to the tradename Cialis. DRUDP did not have any questions at this time and the review is on track for a 10-month action letter.

On 17 January 2002, Lilly ICOS verbally requested a teleconference with Dr. Hirsch to discuss status of NDA review. The FDA review team did not want any "back and forth" communication with the sponsor while they were working on their review.

On 23 January 2002, Lilly ICOS submitted 12 months of stability data for the 20 mg tablets.

On 1 February 2002, Lilly ICOS submitted revised packaging and labeling.

On 6 February 2002, Lilly ICOS submitted updated QTc information per an earlier request from FDA.

In a teleconference on 6 February 2002, the FDA Pharmtox Reviewers requested additional information on the saturation of absorption of the metabolites of IC351.

On 11 February 2002, Lilly ICOS received an Information Request Letter from FDA. There was one question from the Clin Pharm reviewers on metabolites of IC351 and several clarification questions from the CMC reviewers.

In a teleconference on 20 February 2002, Dr Hirsch communicated the status of the NDA review. Dr. Hirsch discussed the following topics: 20 mg dose, tadalafil exposure in renal impaired patients, AE profile, 20 mg clin pharm studies, AE profile in alcohol interaction studies. FDA review was on schedule to meet action date.

On 26 February 2002, Lilly ICOS submitted dissolution data for the 20 mg tablet.

In a teleconference on 4 March 2002, the FDA Pharmtox Reviewer provided feedback on study designs to address saturation of absorption of the metabolites of IC351. Following the teleconference, Lilly ICOS faxed the new study designs which incorporated the changes discussed by FDA. A formal submission was made on 20 March 2002.

On 5 March 2002, Lilly ICOS faxed a document to FDA with rationale for not pursuing a 10 mg strength dose.

On 6 March 2002, Lilly ICOS submitted responses to the Information Request Letter dated 11 February 2002.

On 12 March 2002, Lilly ICOS submitted three documents in response to the 20 February 2002 teleconference: Rationale for 20 mg Starting Dose, Potential for Pharmacodynamic Interaction with alcohol, and Updated Safety Information.

In a teleconference on 22 March 2002, the FDA project manager stated the FDA reviewers were trying to get all the reviews finalized and we would get IR letters if there are any outstanding issues.

On 1 April 2002, Lilly ICOS submitted the proposed Cialis label for Europe as requested.

In a teleconference on 1 April 2002, the FDA CMC reviewer requested some additional information on stability testing and stated the Lilly ICOS proposal for 24 months expiry on the 20 mg tablets was not acceptable. 18-month dating will be granted and can be extended to 24 months in a post approval submission supported by primary stability data. Information requested was submitted on 5 April 2002.

On 4 April 2002, Lilly ICOS submitted a revised container label.

In a teleconference on 11 April 2002, the FDA project manager reported the review team was still in the process of completing their reviews. She indicated the action letter could be an "approvable letter" if there were still unresolved issues.

On 15 April 2002, Greg Brophy (Lilly) sent an e-mail to Dan Shames (FDA) requesting a meeting to discuss the status of the NDA review.

On 16 April 2002, Lilly ICOS submitted the results of the studies to address saturation of absorption of the metabolites of IC351. (This information was not required prior to an approval).

In a meeting on 17 April 2002, Dr. Shames (Acting Division Director) stated labeling will not be discussed by the goal date and whether the "action" will be a "not approval" or "approvable" has not been decided.

In a teleconference on 18 April 2002, Florence Houn (FDA Office Director) conveyed the Action Package was not finalized. She stated an approvable letter was still under discussion. She noted FDA was focused on the following areas: alcohol interaction, nitrate interaction/long half-life, etiology of backpain, QT prolongation.

On 22 April 2002, Lilly ICOS requested a face-to-face meeting with the FDA and submitted a briefing document to address the topics noted in the teleconference with Dr Houn on 18 April 2002.

In a meeting on 23 April 2002, Dr. Shames (Acting Division Director) stated DRUDP will be recommending a "Not approval" based on insufficient evidence to support safety of Cialis. The issues surrounding approval are: QTc, nitrate and alcohol interaction. Additional issues that are not approvability issues are: lowest effective dose, interaction with antihypertensives, effect on vision, long half-life and interaction with BPH alpha blockers.

In a meeting on 26 April 2002, Lilly ICOS and FDA discussed the probable content of the approvable letter. The action letter will state the deficiencies and may suggest a course of action to address the deficiencies.

On 29 April 2002, Lilly ICOS received an Approvable Letter for NDA 21-368. The letter outlined the primary deficiencies, as well as other issues to be addressed by Lilly ICOS, plus a request for updated safety information.

On 3 May 2002, Lilly ICOS submitted our intent to file an amendment in response to the approvable letter per regulations.

On 10 May 2002, Lilly ICOS submitted two protocols, LVDN and LVET for review to address deficiencies #1 nitrate interaction and #2 alcohol interaction respectively.

On 10 May 2002, Lilly ICOS submitted a Type A meeting request to attain a mutually agreed-upon action plan to address the topics identified in the approvable letter.

On 14 May 2002, Lilly ICOS submitted a request for Consult with the Cardio-renal Division.

In a meeting on 20 May 2002, Lilly ICOS discussed expectations of the meeting scheduled for 3 June 2002. FDA stated scientific issues will be discussed, review of the protocols submitted may not be complete by the meeting, questions in the briefing documents will be discussed, labeling will not be discussed.

In a meeting on 3 June 2002, Lilly ICOS and FDA agreed on the approaches to be used to address the topics in the approvable letter. Subsequent to the meeting, protocols to address deficiencies were submitted for review and approval.

On 5 August 2002, Lilly ICOS faxed questions regarding the visual study to be addressed by Dr. Chambers. A teleconference took place on 6 August 2002. Minutes from the meeting were submitted to the NDA on 27 August 2002.

On 6 August 2002, Lilly ICOS submitted study report LVBZ (effect on coronary blood flow) to the NDA in response to the approvable letter.

On 8 August 2002, Lilly ICOS requested a teleconference with the FDA statistician to discuss appropriately defining period of responsiveness and time to onset. The meeting was denied on 29 August 2002. However, a teleconference was then scheduled for 7

October 2002. FDA stated they are uncomfortable with “period of responsiveness”. Language for labeling needs to be explicit of what was observed during the clinical studies.

On 29 August 2002, FDA sent comments on the protocols submitted for review to address the topics in the approvable letter.

On 5 September 2002, Lilly ICOS submitted final versions of the protocols to address the topics in the approvable letter. On 13 December 2002, the FDA project manager telephoned to say all protocols had been reviewed and were found to be acceptable.

On 12 September 2002, Lilly ICOS submitted a QT analysis in response to the approvable letter.

On 27 November 2002, Lilly ICOS submitted a request for a Type C meeting to discuss the NDA review process. A meeting was scheduled for 10 February 2003

On 30 September 2002, Lilly ICOS submitted a Type B meeting request to discuss CMC topics planned for inclusion in the Complete Response. A Briefing Document was submitted 23 October 2002 for the 16 December 2002 meeting.

On 12 November 2002, Lilly ICOS received a copy of the Cardio-renal consult on the reanalysis of the QT data. The consult concluded the data were consistent with ECG data previously reviewed and that there are no indications of an effect on QT by tadalafil. Two weaknesses were pointed out : data based on few subjects, it is not possible to specify what magnitude of mean effect on QT these data exclude.

A meeting took place on 10 February 2003 to discuss the process for review and communications during the review of the Complete Response. Several specific time points for communications were agreed upon at that meeting. These include: Pre-submission meeting, post-submission meeting, 74-day letter, 4-month meeting and label discussions to begin during month 5 of the review.

On 13 February 2003 Lilly ICOS submitted a Type A meeting request for a pre-Complete Response submission meeting. Lilly ICOS stated our intention to submit the Complete Response 11 March 2002. The meeting was scheduled for 4 March 2003. Briefing materials for the meeting were submitted on 17 February 2003.

A meeting took place on 4 March 2003 to address how each of the topics in the approvable letter would be addressed. FDA provided feedback based on the information supplied in the briefing package.

All topics had an appropriate study conducted or would be a review issue. Of note, FDA requested that results from the positive control QT study must be submitted in order to resolve the deficiency.

An agreement was reached on 19 March 2003 for Lilly ICOS to submit results of the positive control QT study (Study LVFB) not more than 1 month after the Complete Response submission. Documentation of the agreement was submitted 25 March 2003.

A teleconference was held on 19 March 2003 regarding the visual effects study, LVFF and implications for class labeling. Also, at that teleconference, further testing of patients who experience back pain was discussed. A summary of this teleconference, and proposal to conduct no further testing of patients who experience back pain was submitted to DRUDP on 16 April 2003.

The re-submission of NDA 21-368 (complete response to the approvable letter) was submitted on 27 May 2003.

A request for a post-submission navigation meeting was submitted to DRUDP on 30 May 2003.

A summary of the results of the QT study (LVFB) was submitted on 17 June 2003.

The final clinical study report for the QT study (LVFB) was submitted on 24 June 2003.

Lilly ICOS submitted a letter to DRUDP outlining two ongoing clinical pharmacology studies to examine the interaction of tadalafil with alcohol and with doxazosin on 26 June 2003.

A navigation meeting to go through the Complete Response was held on 10 July 2003.

A request for a 4-month review meeting was submitted on 15 July 2003.

The Periodic Safety Update Report (PSUR) covering the period October 15, 2002 through April 15, 2003 was submitted to DRUDP on 22 July 2003.

An analysis to support dosing recommendations with ritonavir was submitted to DRUDP on 7 August 2003.

A "74-day letter" providing an update of the review of NDA 21-368 was received by Lilly ICOS from DRUDP on 13 August 2003.

On 19 August 2003, information was submitted in response to a telephone request from one of the medical reviewers at DRUDP.

Lilly ICOS submitted a response to FDA's "74-day letter" on 22 August 2003 (datasets) and 26 August 2003 (other comments).

Lilly ICOS submitted updated datasets for two studies (LVDT and LVFB) on 29 August 2003 as requested by DRUDP.

Lilly ICOS submitted revised trade and sample bottle labels for bottles of 10 mg and 20 mg Cialis on 11 September 2003.

A 4-month review meeting was scheduled for 18 September 2003.

Lilly ICOS sent a proposed agenda and topics for discussion at the 4-month review meeting by secure e-mail on 11 September 2003.

The 4-month review meeting was cancelled on 17 September 2003 because FDA was to be closed on 18 September due to a hurricane.

On 23 September 2003, DRUDP sent to Lilly ICOS by secure e-mail DRUDP's comments on the topics that Lilly ICOS proposed for discussion at the 4-month review meeting. Lilly ICOS submitted responses to these comments by secure e-mail on 26 September 2003.

The 4-month review meeting was held on 30 September 2003. DRUDP provided a status update of the review, and indicated that comments on the USPI would be sent to Lilly ICOS Oct 15-21.

Lilly ICOS sent by secure e-mail on 7 October 2003 minutes of the 30 September meeting.

Lilly ICOS sent requested dissolution data to DRUDP on 9 October 2003.

On 13 October 2003, Lilly ICOS requested a teleconference with the DRUDP chemistry reviewers.

On 13 October 2003, Lilly ICOS submitted a summary of the recent alcohol interaction study, as well as revised proposed label language regarding alcohol.

Lilly ICOS submitted the updated methods validation package on 15 October 2003.

A teleconference to discuss chemistry data requirements was held on 17 October 2003. Lilly ICOS proposed submitting Certificates of Analysis for manufacture of the 5 mg tablets in Puerto Rico. DRUDP requested comparative dissolution data in addition to the Certificates of Analysis. Timing of this submission was to be worked out in the near future.

Lilly ICOS submitted a letter to NDA 21-368 on 20 October 2003 to remove the Indianapolis manufacturing facility from the NDA.

Lilly ICOS submitted further information on 20 October 2003 regarding proposed dosing in patients with renal insufficiency.

Lilly ICOS submitted revised trade and sample bottle labels for 5 mg (trade only), 10 mg, and 20 mg tablets on 24 October 2003.

A teleconference between Lilly ICOS and DRUDP Chemistry Reviewers and DRUDP Review Team Leader was held on 28 October 2003. Agreement was reached regarding submission of information needed for approval of 5 mg tablets.

November 21, 2003 FDA APPROVAL



UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office  
ASSISTANT SECRETARY AND COMMISSIONER  
OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

AUGUST 18, 1997

MARSHALL, O'TOOLE, GERSTEIN  
JAMES J. NAPOLI  
6300 SEARS TOWER  
233 SOUTH WACKER DRIVE  
CHICAGO, IL 60606-6402

PTAS  
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AUG 21 1997



\*100464496A\*

MARSHALL O'TOOLE

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NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

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RECORDATION DATE: 07/14/1997

REEL/FRAME: 8610/0428  
NUMBER OF PAGES: 2

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:

LABORATOIRE GLAXO WELLCOME S.A.

DOC DATE: 06/12/1997

ASSIGNEE:

ICOS CORPORATION, A DELAWARE CORPORATION  
22021 20TH AVENUE, S.E.  
BOTHELL, WASHINGTON 98021

SERIAL NUMBER: 08669389

FILING DATE: 07/16/1996

PATENT NUMBER:

ISSUE DATE:

PEARLENE FOSTER, EXAMINER  
ASSIGNMENT DIVISION  
OFFICE OF PUBLIC RECORDS

# ASSIGNMENT

WHEREAS, the invention or improvements disclosed in the following application was previously assigned by the inventors thereof to the undersigned, and whereas the assignment was recorded as follows:

U.S. Serial No. 08/669,389  
filed July 17, 1996

Reel and Frame unknown--  
(copy of assignment forwarded for  
recording attached)

"TETRACYCLIC DERIVATIVES,  
PROCESS OF PREPARATION  
AND USE"

NOW, THEREFORE, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the undersigned hereby assigns to ICOS Corporation, a Washington corporation, 22021 20th Avenue SE, Bothell, Washington 98021 U.S.A. (hereinafter "Assignee"), its successors and assigns, the entire right, title and interest in the invention or improvements disclosed in the above-mentioned application, and in any applications, both United States and foreign, which the undersigned has filed or may file, either solely or jointly with others, on said invention or improvements, and in any and all Letters Patent of the United States and foreign countries, which have been or may be obtained on any of said applications, and in any reissue or extension thereof.

The undersigned warrant themselves to be the owners of the interest herein assigned and to have the right to make this assignment and further warrant that there are no outstanding prior assignments, licenses, or other rights in the interest herein assigned.

For said consideration the undersigned hereby agree(s), upon the request and at the expense of said assignee, its successors and assigns, to execute any and all divisional, continuation, continuation-in-part and substitute applications for said invention or improvements, and any necessary oath or affidavit relating thereto, and any application for the reissue or extension of any Letters Patent that may be granted upon said application, and any and all applications and other documents for Letters Patent in foreign countries on said invention or improvements, that said assignee, its successors or assigns, may deem necessary or expedient, and for the aforesaid consideration the undersigned further agree(s) upon the request of said assignee, its successors or assigns, in the event of any application or Letters Patent assigned herein becoming involved in Interference, to cooperate to the best of the ability of the undersigned with said assignee, its successors or assigns, in the matters of preparing and executing the preliminary statement and giving and producing evidence in support thereof, the undersigned hereby agreeing to perform, upon request, any and all affirmative acts to obtain said Letters Patent, both United States and foreign, and vest all rights therein hereby conveyed in said assignee, its successors and assigns, whereby said Letters Patent will be held and enjoyed by said assignee, its successors and assigns, to the full end of the term for which said Letters Patent may be granted as fully and entirely as the same would have been held and enjoyed by the undersigned if this assignment and sale had not been made.

WITNESS our hands this 12<sup>th</sup> day of June, Nineteen Hundred and Ninety-seven.

MARSHALL, O'TOOLE, GERSTEIN, MURRAY & BORUN, 6300 Sears Tower, 233 South Wacker Drive, Chicago, Illinois 60606-6402

Witness:

[Signature]

Gab [Signature]

Witness:

[Signature]

Danielle BAYLE

LABORATOIRE GLAXO WELLCOME S.A.,  
(formerly LABORATOIRES GLAXO SA)

By

[Signature]

Name

Philippe Melot

Title

Legal Director

07-30-1997



10045496

To the Honorable Commissioner of Patents and Trademarks: Please record the attached original document or copy thereof.

RECEIVED JUL 14 1997 RECEIPT AND NO. 11

<p>1. Name of party or parties conveying an interest:</p> <p>Laboratoire Glaxo Wellcome S.A.</p> <p style="text-align: center;">MRO 7-14-97</p>	<p>2. Name and address of party or parties receiving an interest:</p> <p>Name: ICOS Corporation, a Delaware corporation Address: 22021 20th Avenue, S.E. City: Bothell State: Washington Zip: 98021</p>
<p>3. Description of the interest conveyed:</p> <p><input checked="" type="checkbox"/> Assignment <input type="checkbox"/> Merger <input type="checkbox"/> Change of Name <input type="checkbox"/> Security Agreement</p> <p>Other: Certificate under 37 CFR 3.73(b) and copy of previous assignment.</p> <p>Execution Date: June 12, 1997</p>	
<p>4. Application number(s) or patent number(s). Additional sheet attached? YES _____ NO <u>X</u></p>	<p>If the document is being filed together with a new application, the execution date of the application is:</p>
<p>A. Patent application no.(s): 08/669,389 filed July 17, 1996</p>	<p>B. Patent no.(s):</p>
<p>5. Name and address of party to whom correspondence concerning this cover sheet should be mailed:</p> <p>Name: James J. Napoli Reg. No. 32,361 MARSHALL, O'TOOLE, GERSTEIN, MURRAY &amp; BORUN Street Address: 6300 Sears Tower, 233 South Wacker Drive City: Chicago State: Illinois Zip: 60606-6402</p>	<p>6. Number of applications and/or patents identified on this cover sheet: <u>1</u></p> <p>7. Amount of fee enclosed or authorized to be charged: \$ 40.00</p> <p>8. Any additional required fee may be charged, or any overpayment credited to our deposit account: 13-2855</p>

9. To the best of my knowledge and belief, the information contained on this cover sheet is true and correct and any copy submitted is a true copy of the original document.

Date: July 11, 1997

James J. Napoli  
James J. Napoli  
Reg. No. 32,361

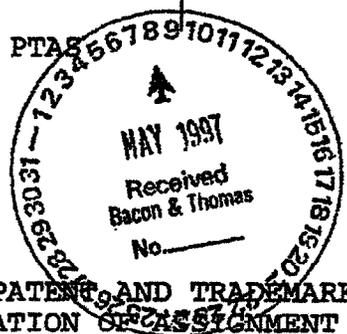
Total number of pages including cover sheet, attachments, and document: 2



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 Washington, D.C. 20231

MAY 05, 1997

BACON & THOMAS  
 RICHARD E. FICHTER  
 625 SLATERS LANE  
 4TH FLOOR  
 ALEXANDRIA, VA 22314



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RECORDATION DATE: 03/10/1997

REEL/FRAME: 8393/0164  
 NUMBER OF PAGES: 2

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:  
 DAUGAN, ALAIN CLAUDE-MARIE

DOC DATE: 12/19/1996

ASSIGNEE:  
 LABORATOIRE GLAXO WELLCOME S.A.  
 43 RUE VINEUSE  
 75116 PARIS, FRANCE

SERIAL NUMBER: 08669389  
 PATENT NUMBER:

FILING DATE: 07/16/1996  
 ISSUE DATE:

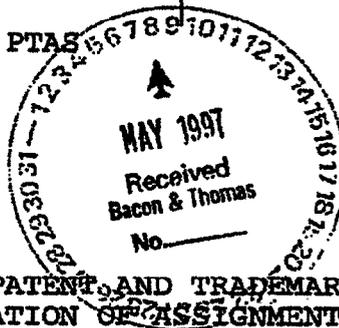
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MAY 05, 1997

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FILING DATE: 07/16/1996  
 ISSUE DATE:

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 ASSIGNMENT DIVISION  
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03-20-1997

U.S. Department of Commerce  
Patent and Trademark Office



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100375481

To the Honorable Commissioner of Patents and Trademarks. Please record the attached original documents or copy thereof.

1. Name of Conveying Party:

Alain Claude-Marie DAUGAN

2. Name and Address of Receiving Party:

Name: Laboratoire Glaxo Wellcome S.A.

Internal Address:

Street Address: 43 Rue Vineuse

City, State, Zip: 75116 Paris, France

3. Nature of Conveyance:

ASSIGNMENT

Execution Date: December 19, 1996

4. (A) Patent Application Number:

08/669,389

4. (B) Patent Number:

If this document is being filed together with a new application, the execution date of the application is:

Additional Numbers Attached.

5. Name and Address of Party to whom Correspondence Concerning this Document Should be Mailed:

Name: Richard E. Fichter, Registration No. 26,382

Address: Bacon & Thomas  
625 Slaters Lane - 4th Floor  
Alexandria, Va 22314

6. Total Number of Applications and Patents Involved:

1

7. Total Fee:

(37 CFR 3.41)

\$40.00

SUBMITTED HEREWITH.

8. Deposit Account Number:

02-0200

ATTACH DUPLICATE COPY OF THIS PAGE IF PAYING BY DEPOSIT ACCOUNT.

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9. Statement and Signature:

To the best of my knowledge and belief, the foregoing is true and correct and any attached copy is a true copy of the original document.

Richard E. Fichter, Reg. No. 26,382  
Name of Person Signing

*Richard E Fichter*  
Signature

March 10, 1997  
Date

Total number of pages comprising cover sheets 28669389

420 W. ...  
1 1997

ASSIGNMENT

WHEREAS, I (we), Alain Claude-Marie DAUGAN  
whose post office address(es) appear(s) below, hereinafter referred to as ASSIGNOR, have invented certain new and  
useful improvements in ... Tetracyclic derivatives, process of preparation and use.....  
for which an application for United States Letters Patent was

- executed on even date herewith;
- executed on \_\_\_\_\_;
- filed on 17 July 1996, Serial No. 08.669389;
- filed as International Application No. PCT/EP95.00183 on 19 January 1995;

and WHEREAS,  
Laboratoire Glaxo Wellcome S.A......

whose post office address is 43 Rue Vinense, 75116 Paris, France hereinafter referred to as ASSIGNEE, is desirous  
of acquiring the entire right, title and interest in and to the same in the United States;

NOW, THEREFORE, for good and valuable consideration, receipt of which is hereby acknowledged, I (we), ASSIGNOR, by these  
presents do sell, assign and transfer unto said ASSIGNEE, the entire right, title, and interest in and to said invention and  
application throughout the United States of America, including any and all Letters Patent granted on any division, continuation,  
continuation-in-part and reissue of said application.

ALSO, ASSIGNOR hereby agrees to execute any documents that legally may be required in connection with the filing,  
prosecution and maintenance of said application or any other patent application(s) in the United States for said invention,  
including additional documents that may be required to affirm the rights of ASSIGNEE in and to said invention, all without  
further consideration. ASSIGNOR also agrees, without further consideration and at ASSIGNEE'S expense, to identify and  
communicate to ASSIGNEE at ASSIGNEE'S request documents and information concerning the invention that are within ASSIGNOR'S  
possession or control, and to provide further assurances and testimony on behalf of ASSIGNEE that lawfully may be required of  
ASSIGNOR in respect of the prosecution, maintenance and defense of any patent application or patent encompassed within the terms  
of this instrument. ASSIGNOR'S obligations under this instrument shall extend to ASSIGNOR'S heirs, executors, administrators and  
other legal representatives.

ASSIGNOR hereby authorizes and requests the Commissioner of Patents and Trademarks to issue any and all Letters Patent  
referred to above to ASSIGNEE, as the ASSIGNEE of the entire right, title and interest in and to the same, for ASSIGNEE'S sole  
use and behoof; and for the use and behoof of ASSIGNEE'S legal representatives and successors, to the full end of the term for  
which such Letters Patent may be granted, as fully and entirely as the same would have been held by ASSIGNOR had this assignment  
and sale not been made.

<i>Assignor name and address</i>	
Alain Claude-Marie DAUGAN Laboratoire Glaxo Wellcome S.A, Centre de Recherches, Z.A. de Courtabœuf, 25 avenue de Quebec, 91940 Les Ulis, France	
Date	<u>19 DEC 1996</u>
Where signed	<u>Les Ulis</u>
Signature	