

**Table 3.H.3. History of Regulatory Correspondence (continued)**

Date	IND Serial # or Type of Communication	Comments
6/28/01	#330 Questions to FDA Regarding Data in NDA	Lilly submitted a proposal as to what data (datasets, type of clinical report, case report forms, patient narratives and patient listings) would constitute the NDA submission for MPM. Lilly asked for FDA feedback on the proposal
7/24/01	FAX to FDA Containing the DSMB Open Report	The DSMB met on 23 July 2001 and concluded unanimously in the Open Report summary that trial JMCH should continue. No safety concerns for the trial were noted. They also strongly recommended that the final primary analysis of JMCH should be on the 329 fully supplemented patients rather than on the total patient population as specified in the study protocol. (see entry below for 20 August 2002)
7/30/01	FAX to FDA	FAX included the following for a teleconference requested ASAP to discuss the finding of particulate matter in LY231514 clinical trial vials under accelerated stability testing conditions. The FAX included the following: <ul style="list-style-type: none"> <li>• Introduction</li> <li>• Background information on glass delamination problem seen during stability testing of liquid formulation of LY231514 at 30°C and 40°C</li> <li>• Discussion of findings</li> <li>• Proposal to switch to lyophilized material for future enrollment.</li> </ul>
7/31/01	FAX sent to FDA	Information requested by the FDA sent via FAX.: <ul style="list-style-type: none"> <li>• Summary of clinical formulations used to date</li> <li>• Table of package components for Development Formulations 2 and 3</li> <li>• Current stability data for Formulations 2 and 3.</li> </ul>
7/31/01	Teleconference Regarding Particulates in CT Material	A teleconference was held to discuss the finding of particulate matter in stability samples of LY231514 clinical trial lots stored at accelerated stability test conditions. Lilly proposed and DODP agreed to replace all solution formulation CT supplies with vials of an earlier freeze-dried formulation to allow the continuation of ongoing clinical trials without interruption. Lilly further committed to not re-introduce the solution formulation product back into clinical studies without first reviewing the supportive data package with the DNDC I personnel.
8/17/01	#340 Protocol Amendment	Protocol amendment JMCH(g) replaced liquid formulation of LY231514 with lyophilized preparation.
8/20/01	#341 Meeting Request	Lilly communicated to FDA the Open Report and Open Minutes from the 23 July DSMB meeting and asked for FDA recommendation as to whether the final analysis for JMCH should be on the total patient population as specified in the protocol or on only the supplemented patient population as the DSMB suggested.

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Table 3.H.3.

## History of Regulatory Correspondence (continued)

Date	IND Serial # or Type of Communication	Comments
8/24/00	#347 Response to FDA Questions	Lilly submitted response to questions asked by FDA in their 07 May 2001 assessment of the 2 <sup>nd</sup> line MPM protocol (JMEW). Protocol JMEW(a) was also submitted.
8/28/01	Letter from Office of Orphan Drugs	LY231514 for MPM indication was granted Orphan Drug designation by the Office of Orphan Drug Products.
9/28/01	FAX from FDA to Lilly	FAX sent from FDA stating that a waiver for the pediatric requirement is not necessary because pediatric waivers do not apply to Orphan drugs
10/5/01	#356 Briefing Document	Lilly provided a briefing document for upcoming 07 November FDA meeting to discuss the patient population to be used for the primary analysis of JMCH. Lilly reiterated to FDA the question as to whether the final analysis for JMCH should be on the total patient population as specified in the protocol or on only the supplemented patient population as the DSMB suggested.
10/25/01	#360 Results of Interim Analysis	Communication to the FDA included the following: <ul style="list-style-type: none"> <li>• Results of the interim analysis of JMCH data in response to the FDA's 23 October 2001 email request (for interim analysis data and DSMB closed meeting minutes). Data was supplied in sealed envelopes to preserve blinding.</li> <li>• Lilly requested FDA's guidance on determination of patient population for JMCH primary analysis of efficacy.</li> </ul>
11/5/01	FDA Communication to Lilly	FDA replied that the patient population for the final analysis of JMCH should be the one specified in the protocol – that is the total patient population. FDA suggested that Lilly might cancel the scheduled 07 November EOP2 meeting. Lilly then requested cancellation of this meeting.
11/20/01	FAX from the FDA to Lilly	FDA completed statistical review of SN 347 (24 August 2000). FDA stated that the SAP (included as part of the protocol) was acceptable and any efficacy claim will be based solely on primary analysis. Covariate-adjusted analysis will be supportive only if primary analysis demonstrates significance and results based on secondary analysis will not be acceptable for efficacy claim.

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**Table 3.H.3. History of Regulatory Correspondence (continued)**

Date	IND Serial # or Type of Communication	Comments
12/14/01	FAX from the FDA to Lilly	FDA completed review of SN 330 (28 June 2001). FDA answered that they agreed with the Lilly proposals regarding electronic datasets, study reports, CRFs, patient narratives, and patient listings, but FDA wants LY231514 + cisplatin trials compiled separate from LY231514 + carboplatin trials, and FDA also wants CRFs for SAE non-drug related patients. FDA reiterated that the 2 <sup>nd</sup> line NSCLC RCT (JMEI) may be necessary to support the MPM trial.
1/30/02	Pre-NDA Meeting	<p>Pre-NDA meeting held for LY231514 MPM indication:</p> <ul style="list-style-type: none"> <li>• Indication based on available data will be LY231514 in combination with cisplatin is indicated for advanced MPM</li> <li>• Final analysis plan is acceptable</li> <li>• LY231514 + cisplatin safety data should have both combined and separate analyses</li> <li>• Unless the single RCT (JMCH) has highly significant survival outcome, it is not sufficient. A 2<sup>nd</sup> line NSCLC trial may be necessary for support of NDA</li> <li>• Response rate is not acceptable primary endpoint in MPM</li> <li>• Nonclinical and ADME packages are acceptable</li> <li>• FDA requested preclinical metabolism/in vitro P-450 studies also be included in human PK section.</li> </ul>
3/19/02	#394 Request Meeting MPM NDA	Lilly requested a meeting to discuss the final results of JMCH and to ask FDA if there was sufficient evidence to file the NDA based on a single trial. Lilly also asked FDA if they would support Fast Track designation for LY231514 in MPM to allow for a rolling NDA.
3/26/02	SN 396	Lilly notified FDA that its development efforts to resolve the glass delamination problem seen with the solution formulation were unsuccessful. Lilly confirmed its intention to focus all development efforts on commercialization of the stable lyophilized formulation. This correspondence requested a CMC pre-NDA meeting to discuss a proposed drug product data package consisting of extensive supporting clinical trial stability lots and limited primary stability data.

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Table 3.H.3.

## History of Regulatory Correspondence (continued)

Date	IND Serial # or Type of Communication	Comments
3/29/02	FDA response to Lilly regarding Lilly's Meeting Request	FDA answered that the increased survival observed in JMCH would support an NDA filing based on a single registration trial. FDA also stated they would support Fast Track designation and a rolling submission for the LY231514 MPM NDA (and that provisions related to accelerated approval based on surrogate endpoint would not apply to a drug that approves regular approval). FDA expressed their interest in reviewing follow-up scans for response determination. FDA also stated that they would like to see the "Protocol for Treatment" operational before the ASCO proceedings were made public.
4/8/02	#408	Lilly requested that FDA comment on the "Protocol for Treatment" (Study JMFE) that would allow MPM patients expanded access to LY231514. Lilly asked FDA if they would respond telling Lilly if it could proceed with trial JMFE.
4/10/02	#402 Request for Fast-Track	Based on FDA's response of 29 March 2002 supporting Lilly's request for Fast Track Designation for LY231514 in MPM, Lilly submitted a formal request for Fast Track Designation.
04/12/02	SN 405 CMC Pre-NDA Meeting Package	Lilly submitted a CMC briefing document outlining the proposed drug product data package for the lyophilized formulation in advance of the scheduled May 15, 2002 pre-NDA meeting. This submission contained comparative information of the supporting CT stability and proposed commercial lyophilized lots, the proposed NDA supporting and primary stability data package, and proposed stability protocols for the primary stability batches.
4/15/02	#406 Preclinical Tumor Xenograft findings	Lilly informed FDA that two of the late preclinical reports (NCPR-9 and NCPR-10) could not be substantiated. Although these reports would be included in the NDA for completeness, they would not be integrated nor discussed. As a follow-up to this issue, personnel and other changes have been made in the laboratory that performed these studies.
5/03/02	Lilly email to Ms. Debbie Vause @ FDA	Jeff Ferguson, Lilly CMC regulatory, submitted an email to Ms. Debbie Vause, FDA project manager for LY231514 submissions, outlining a proposed rolling submission timeline and content for discussion during the upcoming May 15, 2002 CMC teleconference (reference 12 April 2002 briefing document: SN 405). The goal was to obtain FDA input on what would constitute a reviewable CMC unit for FDA.

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Table 3.H.3.

## History of Regulatory Correspondence (continued)

Date	IND Serial # or Type of Communication	Comments
5/9/02	#415 JMFE Protocol Submitted	Final version of JMFE protocol submitted (see SN 408 on 4 Apr 2002). FDA's comments and suggestions were addressed in this final version. Lilly informed FDA that MPM patients unsuitable for participation in JMFE will be referred to the FDA with requests for Single Patient Use INDs
5/15/02	#416 Communication on 2 <sup>nd</sup> Line MPM	Lilly informed FDA that it does plan to conduct an additional trial in 2 <sup>nd</sup> line MPM patients at this time.
5/15/02	FDA pre-NDA CMC teleconference	Lilly and FDA DNDC-I staff held a CMC teleconference to review the proposals outlined in Lilly's briefing document dated 12 April 2002 (SN 405) and Lilly FAX dated 03 May 2002. FDA comment that the proposed NDA supporting and primary stability data package, and proposed stability protocols for the primary stability batches seemed reasonable. FDA further provided guidance regarding appropriate content of reviewable units submitted under the rolling submission provisions of a priority review.
5/23/02	FDA FAX to Lilly	FDA faxed to Lilly FDA's official minutes from the 15 May 2002 CMC teleconference.
6/10/02	Letter from FDA to Lilly	FDA granted Fast Track designation for LY231514 for MPM and agreed to a step-wise ("rolling") submission.
6/14/02	FAX from FDA to Lilly	FDA (Division of Medication Errors and Technical Support) completed preliminary review and has no objection to the use of the proprietary name LY231514.
8/8/02	#444	Lilly submitted the Briefing Document for the 06 September pre-NDA meeting to discuss the details of the proposed rolling submission. This document included questions for the FDA.

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**Table 3.H.3. History of Regulatory Correspondence (continued)**

Date	IND Serial # or Type of Communication	Comments
9/6/02	Pre-NDA Meeting to Discuss Rolling Submission	<p>FDA and Lilly agreed that DODP is willing to review a MPM indication based on a single trial, and the study would lend to approval with the support of a 2<sup>nd</sup> study (in NSCLC). However, this does not set a precedent. For Stage A of the rolling submission, FDA expects the draft label, the PK data and the study reports for JMCH and JMDR. For Stage B FDA expects the ISS, the ISE and the final label. Lilly will provide during the rolling NDA the CT scanned images for responders at baseline and at best response in Study JMCH. Lilly will provide a proposal for an LY231514 plus cisplatin versus LY231514 trial in 2<sup>nd</sup> line and beyond patients and Lilly will request a meeting to discuss this trial. For Stage C, FDA expects the complete API sections and expects the API manufacturing sites to be PAI ready at the time of submission. For Stage D, FDA agreed to the data package and content outlined in the 08 August 2002 briefing document (SN 444) and emphasized that the drug product manufacturing sites should be PAI ready at submission. FDA expressed concern over the change in container closure suppliers and requested that Lilly submit data package supporting this change and schedule a teleconference to discuss this issue before submission of Stage C or D.</p>
10/18/02	#463 Rolling Submission Timelines	<p>Lilly submitted plans for the rolling submission timeline for the LY231514 MPM NDA.</p>
10/30/02	Teleconference between Lilly and FDA	<p>Discussion on the randomized trial of LY231514 plus cisplatin versus cisplatin in MPM being requested by FDA. FDA stated that a new trial in first line MPM is necessary. The following agreements were reached:</p> <ul style="list-style-type: none"> <li>• The trial design is LY231514 plus cisplatin versus either LY231514 plus carboplatin or LY231514 + gemcitabine.</li> <li>• Trial to be run as an intergroup trial with cooperative groups.</li> <li>• The existing expanded access "Protocol for Treatment" (JMFE) will be amended to include previous pretreated MPM patients.</li> </ul>

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Table 3.H.3.

## History of Regulatory Correspondence (concluded)

Date	IND Serial # or Type of Communication	Comments
12/02/02	#478	As agreed during the 06 September 2002 pre-NDA (rolling submission) meeting, Lilly requested a teleconference with the DNDC-I personnel and provided a briefing document outlining the comparability and compatibility data generated to support the change to a comparable container closure system sourced from European suppliers. This change was necessitated by Lilly's need to transfer the commercial manufacturing operations to its Fegersheim, France commercial manufacturing site. The goal of this meeting was to obtain FDA input on the CMC information and data contained in this briefing document and confirm that the data will be sufficient to support the proposed change in container closure system.
12/3/02	Meeting with FDA for 45 Day Presentation	Lilly gave a 45 day presentation to DODP with the rationale as to why the LY231514 MPM NDA should be approved.
12/17/02	FDA CMC Teleconference	During this CMC teleconference, FDA confirmed that the data provided in the briefing document comparing the two container closure systems was adequate to support the change to alternate European component suppliers for the commercial product. FDA therefore confirmed that the data from the CT stability lots using US component suppliers was considered support. Resolution of this one outstanding issue resulted in DNDC-I acceptance of the proposed drug product submission package outlined in Lilly's briefing document dated 08 August 2002 (SN 444).
12/20/02	#488	Lilly submitted a copy of its internal minutes to the 17 December 2002 CMC teleconference.
01/14/03	FDA email from Dorothy Pease	Dorothy Pease, FDA Supervisory Project Manager, submitted an email dated 14 January 2003 to Jeff Ferguson at Lilly containing the FDA minutes to the 17 December 2002 teleconference.
2/5/03	#498	Lilly submitted amendment JMFE(b) allowing for treatment of second-line and beyond MPM patients with either LY231514 plus cisplatin or single agent LY231514 in the expanded access "Protocol for Treatment." The protocol was also changed such that patients with "malignant mesothelioma" were now eligible as compared to "malignant pleural mesothelioma" in previous versions of the protocol.

EXHIBIT XI

SECOND AMENDMENT TO AGREEMENT

AMENDMENT dated as of March 11, 2004, to the Agreement dated December 19, 1985, between the TRUSTEES OF PRINCETON UNIVERSITY, a not-for-profit private educational institution duly organized and existing under the laws fo the State of New Jersey and having a principal place of business in Princeton, New Jersey 08540, United States of America, (hereinafter "PRINCETON") and ELI LILLY AND COMPANY, a corporation duly organized and existing under the laws of Indiana and having a principal place of business in Indianapolis, Indiana, 46285, (hereinafter "LILLY").

W I T N E S S E T H

WHEREAS, the Parties have entered into the Agreement and would like to amend the Agreement;

WHEREAS, the Parties now seek to amend and update the terms of the Agreement as set forth herein.

NOW THEREFORE, in consideration of the premises and the mutual covenants contained herein, the Parties agree to as follows:

2. Article 11.1 shall be restated in its entirety as follows:

11.1 Post Patent Issuance. After first obtaining consent of PRINCETON, which consent shall not be unreasonably withheld, LILLY will have the right to obtain and enforce any post patent issuance rights relating to any patent covering Licensed Products, including filing and obtaining patent term extensions and SPC's; instituting, prosecuting and controlling foreign actions involving regulatory and intellectual property agencies; and executing foreign powers of attorney on behalf of LILLY and PRINCETON for such actions. LILLY will promptly notify PRINCETON of any such filings or actions and PRINCETON will use all reasonable efforts to assist and cooperate with LILLY with regard to such filings or actions. LILLY will bear its own costs and expenses and PRINCETON's reasonable costs and expenses relating to such filings or actions.

IN WITNESS WHEREOF, the parties hereto have executed this agreement, in duplicate originals, by their respective officers thereunto duly authorized, the day and year hereinafter written.

LILLY

BY:

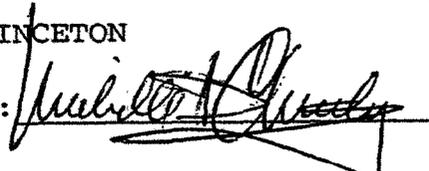


Dr. Paolo Paoletti  
Vice President,  
Medical Oncology

DATED: MARCH 3, 2004

PRINCETON

BY:



DATED: 3/1/04

**Supplemental Exhibit B:  
Patent Term Extension Calculation for Pemetrexed Disodium**

<b>Patent Extension Calculation</b>	<b>Calculations</b>
Date IND Becomes Effective	September 10, 1992
Date NDA Submitted to the FDA	September 29, 2003
Date NDA Approved by the FDA	February 4, 2004
Patent Issue Date	September 6, 1994
U.S. Non-provisional Effective Patent Filing Date	December 11, 1989
U.S. Non-provisional Actual Patent Filing Date	March 22, 1991
Patent Terminal Disclaimer Date (As Applicable)	NA
17 Years from Issue Date	September 6, 2011
20 Years from Filing Date	December 11, 2009
Greater of 17 Years from Issue or 20 Years from Filing	September 6, 2011
Greater of 17/20 Year Terms, If Applicable and Longer	September 6, 2011
Actual Patent Term (Including Applicable Disclaimer)	September 6, 2011
Post-Patent Issuance Start of Regulatory Review	September 6, 1994
Date of Disclaimer for 2-Year Transitional Provision	September 24, 1984
Revised Start Date (Including Applicable Disclaimer)	September 6, 1994
Total Post-9/9/84 IND Review Period (days)	3,310
Start Date of IND Deduction	
End Date of IND Deduction	
Further IND Deduction (days)	0
Net IND Period	3,310
1/2 IND Review Period (days)	1,655
NDA Review Period (days)	129
Regulatory Review Period (days)	3,439
NDA Period + 1/2 IND Period (days)	1,784
Expiration Date of 5 Year Limitation Period	September 6, 2016
Five Year Limitation Period in Days	1,827
Maximum Extension Period Before 14 Year Limit	1,784
Expiration Date Before Applying 14 Year Limit	July 25, 2016
Expiration of 14 Years from NDA Approval	February 4, 2018
Expiration Date As Extended	July 25, 2016
<b>Statutory Extension Period in Days</b>	<b>1,784</b>