

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-677

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

ITEM 14: PATENT CERTIFICATION**NDA 21-677
ALIMTA[®]
(pemetrexed)**

Eli Lilly and Company claims a five year period of exclusivity for the use of ALIMTA as provided by C.F.R. 314.108(b)(2). As evidenced by the absence in the Orange Book that ALIMTA has previously been approved by the FDA, to the best of Applicant's knowledge and belief, ALIMTA has not previously been approved under section 505(b) of the FDCA. Accordingly, Eli Lilly and Company submits ALIMTA as a new chemical entity entitled to a five year period of exclusivity as provided by FDCA 505(c)(3)(D)(ii) and 505(j)(4)(D)(ii)(21 U.S.C. 355(c)(3)(D)(ii) and 355(j)(4)(D)(ii)).

D. Roychowdhury MD
Name of authorized official
Director, US Regulatory Affairs
DEBASISH F. ROYCHOWDHURY, MD

September 25, 2003

Date

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

21-677

NAME OF APPLICANT / NDA HOLDER

Eli Lilly and Company

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ALIMTA

ACTIVE INGREDIENT(S)

Pemetrexed disodium

STRENGTH(S)

vials containing the equivalence of 500 mg pemetrexed

DOSAGE FORM

sterile lyophilized powder for intravenous infusion

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
5,217,974

b. Issue Date of Patent
6/8/1993

c. Expiration Date of Patent
3/29/2011

d. Name of Patent Owner
Eli Lilly and Company

Address (of Patent Owner)
P.O. Box 6288

City/State
Indianapolis, IN

ZIP Code
46206-6288

FAX Number (if available)
317-276-3861

Telephone Number
317-276-2958

E-Mail Address (if available)
patents@lilly.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)
P.O. Box 6288

City/State
Indianapolis, IN

ZIP Code
46206-6288

FAX Number (if available)
317-276-3861

Telephone Number
317-276-2958

E-Mail Address (if available)
patents@lilly.com

General Patent Counsel,
Eli Lilly and Company

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

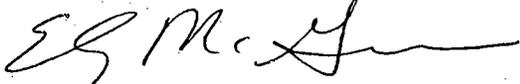
- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) 8 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
Premedication Regimen
Vitamin Supplementation — To reduce toxicity, patients treated with ALIMTA must be instructed to take a low dose oral folic acid preparation or multivitamin with folic acid on a daily basis.
- 4.2 Patent Claim Number (as listed in the patent) 11 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
Premedication Regimen
Vitamin Supplementation — To reduce toxicity, patients treated with ALIMTA must be instructed to take a low dose oral folic acid preparation or multivitamin with folic acid on a daily basis.

4.2 Patent Claim Number (as listed in the patent) 12	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Premedication Regimen Vitamin Supplementation — To reduce toxicity, patients treated with ALIMTA must be instructed to take a low dose oral folic acid preparation or multivitamin with folic acid on a daily basis.
4.2 Patent Claim Number (as listed in the patent) 16	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Premedication Regimen Vitamin Supplementation — To reduce toxicity, patients treated with ALIMTA must be instructed to take a low dose oral folic acid preparation or multivitamin with folic acid on a daily basis.
4.2 Patent Claim Number (as listed in the patent) 18	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Premedication Regimen Vitamin Supplementation — To reduce toxicity, patients treated with ALIMTA must be instructed to take a low dose oral folic acid preparation or multivitamin with folic acid on a daily basis.
4.2 Patent Claim Number (as listed in the patent) 19	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Premedication Regimen Vitamin Supplementation — To reduce toxicity, patients treated with ALIMTA must be instructed to take a low dose oral folic acid preparation or multivitamin with folic acid on a daily basis.
4.2 Patent Claim Number (as listed in the patent) 20	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) Premedication Regimen Vitamin Supplementation — To reduce toxicity, patients treated with ALIMTA must be instructed to take a low dose oral folic acid preparation or multivitamin with folic acid on a daily basis.
5. No Relevant Patents	
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. <input type="checkbox"/> Yes	

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed
	9-3-2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input checked="" type="checkbox"/> Patent Owner	<input checked="" type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Elizabeth A. McGraw	
Address P.O. Box 6288	City/State Indianapolis, IN
ZIP Code 46206-6288	Telephone Number 317-277-7443
FAX Number (if available) 317-276-3861	E-Mail Address (if available) patents@lilly.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use**

NDA NUMBER

21-677

NAME OF APPLICANT / NDA HOLDER

Eli Lilly and Company

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ALIMTA

ACTIVE INGREDIENT(S)

Pemetrexed disodium

STRENGTH(S)

vials containing the equivalence of 500 mg pemetrexed

DOSAGE FORM

sterile lyophilized powder for intravenous infusion

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1 GENERAL

a. United States Patent Number
5,344,932

b. Issue Date of Patent
9/6/1994

c. Expiration Date of Patent
9/6/2011

d. Name of Patent Owner
Princeton University

Address (of Patent Owner)
4 New South Bldg

City/State
Princeton, NJ

ZIP Code
08544

FAX Number (if available)
609-258-1159

Telephone Number
609-258-1570

E-Mail Address (if available)
Jritter@Princeton.edu

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)
P.O. Box 6288

City/State
Indianapolis, IN

ZIP Code
46206-6288

FAX Number (if available)
317-276-3861

Telephone Number
317-276-2958

E-Mail Address (if available)
patents@lilly.com

General Patent Counsel,
Eli Lilly and Company

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in manufacture, use, or sale of the drug product. Yes

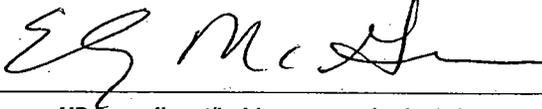
6 Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



9-3-2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Elizabeth A. McGraw

Address
P.O. Box 6288

City/State
Indianapolis, IN

ZIP Code
46206-6288

Telephone Number
317-277-7443

FAX Number (if available)
317-276-3861

E-Mail Address (if available)
patents@lilly.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)**

MEMO OF FILING MEETING

DATE: December 19, 2003

BACKGROUND

Currently, NDA 21-462 Alimta is under review with the Division for pleural malignant mesothelioma.

ATTENDEES: Richard Pazdur, MD
John Johnson, MD
Martin Cohen, MD
Rajeshwari Sridhara, PhD
Yong-Cheng Wang, PhD
ShengHui Tang, PhD
Lilia Talarico, MD
Patty Garvey, R.Ph.

ASSIGNED REVIEWERS:

Discipline	Reviewer
Medical:	Martin Cohen, MD
Secondary Medical:	-----
Statistical:	ShengHui Tang, PhD
Secondary Statistical:	Yong-Cheng Wang, PhD
Pharmacology:	Doo Y. Lee Ham, Ph.D
Statistical Pharmacology:	-----
Chemist:	Chengyi Liang, Ph.D.
Environmental Assessment (if needed):	
Biopharmaceutical:	Brian Booth, Ph.D.
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	David Gans, MD
Project Manager:	Patty Garvey, R.Ph.
Other Consults:	NO

Per reviewers, all parts in English, or English translation? YES X NO

CLINICAL – File X Refuse to file

Clinical site inspection needed: **To be determined** YES _____ NO _____

MICROBIOLOGY CLINICAL – File _____ Refuse to file _____

STATISTICAL – File X Refuse to file _____

BIOPHARMACEUTICS – File X Refuse to file _____

Biopharm. inspection Needed: YES _____ NO _____

PHARMACOLOGY – File X Refuse to file _____

CHEMISTRY – File X Refuse to file _____

Establishment(s) ready for inspection? **Inspection not needed** YES _____ NO _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ The application is unsuitable for filing. Explain why:

Regulatory Project Manager, HFD-150

DISCUSSION: This will be a standard review – PDUFA 9/4/04
ODAC – to be determined, if going to ODAC will be in the summer session

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

/s/

Patricia Garvey
12/23/03 12:58:24 PM
CSO

EXCLUSIVITY SUMMARY for NDA # 21-677 SUPPL #

Trade Name ALIMTA Generic Name pemetrexed

Applicant Name Eli Lilly & Company HFD- 150

Approval Date August 19, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA? YES/X/ NO /___/

b) Is it an effectiveness supplement? YES /___/ NO /X/

If yes, what type(SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 Years

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

YES / / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES / / NO / /

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-462 pemetrexed

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # H3E-MC-JMEI

Investigation #2, Study # H3E-MC-JMBR

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # H3E-MC-JMEI

Investigation #2, Study # H3E-MC-JMBR

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 40-061 YES /_X_/ ! NO /___/ Explain:
!
!
!
!

Investigation #2 !
!
IND # 40-061 YES /_X_/ ! NO /___/ Explain:
!
!
!
!
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!

!

!

Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!

!

!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

Patty Garvey , R.Ph.
Regulatory Project Manager

8-19-04
Date

Richard Pazdur, M.D.
Director
Division of Oncology Drug Product

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

Patty Garvey, R.Ph.
Regulatory Project Manager

8-19-04
Date

Richard Pazdur, M.D.
Director
Division of Oncology Drug Product

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Richard Pazdur
8/19/04 10:48:34 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-677 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: November 4, 2003 Action Date: September 4, 2004

HFD-150 Trade and generic names/dosage form: ALIMTA® (pemetrexed for injection)

Applicant: Eli Lilly and Company Therapeutic Class: Cytotoxic Antimetabolite

Indication(s) previously approved: Treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval

Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-677
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA ###-###-###
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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

/s/

Patricia Garvey
4/22/04 10:40:16 AM

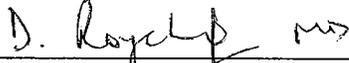
Debarment Certification

NDA Application No.: 21-677

Drug Name: **Alimta (Pemetrexed)**

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Debasish F. Roychowdhury, M.D., hereby certifies that it did not knowingly and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: 
Debasish F. Roychowdhury, M.D.

Title: Director, U.S. Regulatory Affairs

Date: September 18, 2003

See Note to File on Disqualification

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285 c/o Debasish F. Roychowdhury, M.D. Director, U.S. Regulatory Affairs-Oncology		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER NDA 21-677	
2. TELEPHONE NUMBER (Include Area Code) (317) 433-6604		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA).	
3. PRODUCT NAME Alimta (pemetrexed)		6. USER FEE I.D. NUMBER 4576	

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 and 12420 Parklawn Drive, Room 3046 Rockville, MD 20852	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
--	--	--

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 	TITLE Debasish Roychowdhury, M.D. Director, U.S. Regulatory Affairs	DATE September 18, 2003
--	---	----------------------------

Spillman, Dianne D

From: publicpolicy@asco.org [legislative-asco@xmr3.com]
Sent: Thursday, August 19, 2004 3:38 PM
To: spillmand@cder.fda.gov
Subject: FDA approves Alimta for 2nd-line NSCLC

From ASCO Cancer Policy and Clinical Affairs
From the American Society of Clinical Oncology.
In collaboration with the Food and Drug Administration (FDA), and as a service to our members, ASCO will provide information about newly approved therapies for cancer patients. This will allow the agency to inform oncologists and professionals in oncology-related fields of recent approvals in a timely manner. Included in the email from the FDA will be a link to the product label, which will provide the relevant clinical information on the indication, contraindications, dosing, and safety. The following is a message from Dr. Richard Pazdur:

To: ASCO membership (domestic USA, embargo date 8/19/04)

From: Richard Pazdur, M.D.

Director, Division of Oncology Drug Products,
Center for Drug Evaluation and Research, FDA

On August 19, 2004, the U.S. Food and Drug Administration granted accelerated approval to pemetrexed for injection (Alimta®, Eli Lilly and Company) as a singleagent for the treatment of patients with locally advanced or metastatic nonsmall cell lung cancer after prior chemotherapy.

Safety and efficacy were demonstrated in one multi-center, randomized trial in 571 patients comparing single-agent Alimta versus docetaxel. Alimta, 500 mg/m² intravenously, was administered over 10 minutes on day 1 of each 21-day cycle. Patients receiving Alimta also received dexamethasone for skin rash prophylaxis and vitamin B12 and folic acid supplementation.

The primary efficacy endpoint was survival. Alimta failed to demonstrate superior survival compared to docetaxel. Non-inferiority for overall survival could not be demonstrated because there was only one small historical study (total 104 patients) from which to estimate docetaxel's survival effect. A meta-analysis of multiple historical studies is usually required for this survival effect estimation. In addition, comparison of the survival effect in the current randomized trial was confounded by a 32% crossover rate of Alimta patients to docetaxel after tumor progression. The median survival time was 8.3 months for Alimta-treated patients and 7.9 months for docetaxel-treated patients. Secondary efficacy endpoints included response rate (Alimta 9.1%, docetaxel 8.8%), progression-free survival (Alimta and docetaxel, medians 2.9 months) and time-to-progressive disease (Alimta, median 3.4 months; docetaxel, median 3.5 months).

Alimta has a more favorable safety profile than docetaxel. Alimta caused less neutropenia, febrile neutropenia, neutropenic infections and need for granulocyte/macrophage colony stimulating factors. Alimta causes less severe alopecia. Elevation of hepatic transaminases was more frequent with Alimta than docetaxel. Accelerated approval was based on the improved safety profile and effects on surrogate endpoints.

As a condition of accelerated approval, the applicant is required to conduct additional studies to demonstrate a clinical benefit, such as increased survival or improved disease-related symptoms.

Full prescribing information, including clinical trial information, safety, dosing, drug-drug interactions and contraindications is available at www.fda.gov/cder/foi/label/2004/021677lbl.pdf.

"ASCO periodically e-mails its membership messages of professional interest. If you would prefer not to receive these messages, reply to this e-mail with the word REMOVE in the subject field. You will receive one additional e-mail message to confirm your removal from this e-mail list."

If you would prefer not to receive further messages from this sender, please click on the following Internet link and confirm your request:

<http://www.xmr3.com/rm/772958-4876369-2-12994-US1-96F6/spillmand@cderr.fda.gov/HCSCECD>

You will receive one additional e-mail message confirming your removal.

Garvey, Patricia

From: Garvey, Patricia
Sent: Thursday, August 12, 2004 4:57 PM
To: John F Worzalla
Cc: 'Debasish Roychowdhury'; Garvey, Patricia
Subject: RE: Post marketing commitments (Alimta NDA 21-677)

John,

The clinical team has review the below studies for the post-marketing commitments. They studies are acceptable. However, study H3SE-MC-JMGX should be a Phase 4 commitment, but it need not be a required Phase 4 commitment for accelerated approval. The results of this study are not likely to be sufficient to convert the AA to regular approval. The other two studies are required Phase 4 commitments for accelerated approval.

Please let me know if you have any questions.

Patty

-----Original Message-----

From: Debasish Roychowdhury [mailto:ROYCHOWDHURY_DEBASISH@LILLY.COM]
Sent: Tuesday, August 03, 2004 5:21 PM
To: GarveyP@cder.fda.gov
Cc: John F Worzalla
Subject: Post marketing commitments (Alimta NDA 21-677)

Patty:

Here are the details on the post marketing commitment studies that Dr. Pazdur referred to at ODAC. Please let me know if you need any more details or need clarifications on any of the studies and timelines.

Thanks you and hope your son is better.

Debasish

Office: 317 433 6604

Cell: 317 332 4268

H3E-MC-JMGX:

Multicenter, Randomized Phase III Trial of Alimta 500 mg/m² versus 900 mg/m² in Patients with Locally Advanced or Metastatic (Stage III or Stage IV) Non-Small Cell Lung Cancer Who Have Been Previously Treated With Chemotherapy

Status: Actively enrolling with approximately 22/1000 patients enrolled globally.

Last patient visit: December 2006

Final study report: May 2007

H3E-MC-JMDB:

Multicenter, Randomized Phase III Trial of ALIMTA[®] and Cisplatin Versus GEMZAR[®] and Cisplatin in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer

Status: Recently began enrolling. There are approximately 3/1700 patients enrolled.

Last patient visit: June 2008

Final study report: November 2008

8/12/2004

Garvey, Patricia

From: Johnson, John R
Sent: Saturday, August 07, 2004 9:16 AM
To: Garvey, Patricia; Cohen, Martin H
Subject: RE: Post marketing commitments (Alimta NDA 21-677)

Upon reflection study H3SE-MC-JMGX should be a Phase 4 commitment, but it need not be a required Phase 4 commitment for accelerated approval. The results of this study are not likely to be sufficient to convert the AA to regular approval. The other two studies are required Phase 4 commitments for accelerated approval.

John

-----Original Message-----

From: Garvey, Patricia
Sent: Wednesday, August 04, 2004 9:39 AM
To: Cohen, Martin H
Cc: Johnson, John R
Subject: FW: Post marketing commitments (Alimta NDA 21-677)

Hello John and Marty

Below are the details for studies for the phase 4 commitments for Alimta. Please let me know if you need any additional information.

Thanks,
Patty

-----Original Message-----

From: Debasish Roychowdhury [mailto:ROYCHOWDHURY_DEBASISH@LILLY.COM]
Sent: Tuesday, August 03, 2004 5:21 PM
To: GarveyP@cder.fda.gov
Cc: John F Worzalla
Subject: Post marketing commitments (Alimta NDA 21-677)

Patty:

Here are the details on the post marketing commitment studies that Dr. Pazdur referred to at ODAC. Please let me know if you need any more details or need clarifications on any of the studies and timelines.

Thanks you and hope your son is better.

Debasish

Office: 317 433 6604

Cell: 317 332 4268

H3E-MC-JMGX:

Multicenter, Randomized Phase III Trial of Alimta 500 mg/m² versus 900 mg/m² in Patients with Locally Advanced or Metastatic (Stage III or Stage IV) Non-Small Cell Lung Cancer Who Have Been Previously Treated With Chemotherapy

Status: Actively enrolling with approximately 22/1000 patients enrolled globally.

Last patient visit: December 2006

Final study report: May 2007

H3E-MC-JMDB:

Multicenter, Randomized Phase III Trial of ALIMTA[®] and Cisplatin Versus GEMZAR[®] and Cisplatin in Patients

8/10/2004

with Locally Advanced or Metastatic Non-Small Cell Lung Cancer

Status: Recently began enrolling. There are approximately 3/1700 patients enrolled.

Last patient visit: June 2008

Final study report: November 2008



Garvey, Patricia

From: Debasish Roychowdhury [ROYCHOWDHURY_DEBASISH@LILLY.COM]
Sent: Tuesday, August 03, 2004 5:21 PM
To: GarveyP@cder.fda.gov
Cc: John F Worzalla
Subject: Post marketing commitments (Alimta NDA 21-677)

Patty:

Here are the details on the post marketing commitment studies that Dr. Pazdur referred to at ODAC. Please let me know if you need any more details or need clarifications on any of the studies and timelines.

Thanks you and hope your son is better.

Debasish

Office: 317 433 6604

Cell: 317 332 4268

H3E-MC-JMGX:

Multicenter, Randomized Phase III Trial of Alimta 500 mg/m² versus 900 mg/m² in Patients with Locally Advanced or Metastatic (Stage III or Stage IV) Non-Small Cell Lung Cancer Who Have Been Previously Treated With Chemotherapy

Status: Actively enrolling with approximately 22/1000 patients enrolled globally.

Last patient visit: December 2006

Final study report: May 2007

H3E-MC-JMDB:

Multicenter, Randomized Phase III Trial of ALIMTA[®] and Cisplatin Versus GEMZAR[®] and Cisplatin in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer

Status: Recently began enrolling. There are approximately 3/1700 patients enrolled.

Last patient visit: June 2008

Final study report: November 2008



**Quick Minutes
Oncologic Drugs Advisory Committee Meeting
July 27th, 2004**

The following is an internal report which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at <http://www.fda.gov/ohrms/dockets/ac/cder03.htm#Oncologic>.

Slides of the meeting will be available at least 2 – 3 business days after the meeting.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

Prior to the meeting, the members and the invited consultants were provided the background material from the FDA & Sponsor. The meeting was called to order by Otis Brawley, M.D. (Acting ODAC Chair).

The conflict of interest statement was read into the record by Johanna Clifford, M.S., R.N. (Executive Secretary, ODAC). There were approximately 120 persons in attendance.

There was one speaker scheduled for the Open Public Hearing session.

Attendance:

Oncologic Drugs Advisory Committee Members Present (voting)

Otis Brawley, M.D. (Acting Chair), Ronald Bukowski, M.D., Bruce Cheson, M.D., James Doroshow, M.D., Stephen George, Ph.D., Pamela Haylock, RN, Maha Hussain, M.D., Alexandra Levine, M.D., Joanne Mortimer, M.D., Michael Perry, M.D., Maria Rodriguez, M.D.

Oncologic Drugs Advisory Committee Members Absent

Silvana Martino, D.O., Gregory Reaman, M.D.

Oncologic Drugs Advisory Committee Member (non-voting)

Antonio Grillo-Lopez, M.D. (Industry Representative)

Oncologic Drugs Advisory Committee Participants (voting)

Ralph D'Agostino, Ph.D., Sheila Ross (patient representative)

FDA Participants

Robert Temple, M.D., Richard Pazdur, M.D., Martin Cohen, M.D., Yong-Cheng Wang, Ph.D.

Open Public Hearing Speaker:

1. Michelle Pollack, The Wellness Community
-

Issue:

New Drug Application (NDA) 21-677, ALIMTA (pemetrexed) Eli Lilly, Incorporated, proposed indication for single-agent treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.

The agenda was as follows:

Call to Order and Introductions	Otis Brawley, M.D. Acting Chair, Oncologic Drugs Advisory Committee, ODAC
Conflict of Interest Statement	Johanna Clifford, M.S., R.N. Executive Secretary, ODAC
Welcome and Introductory Comments	Richard Pazdur, M.D. Director, Division of Oncologic Drug Products (DODP), FDA

Sponsor Presentation

Introduction and Objectives of the Presentation	Paolo Paoletti, M.D., Eli Lilly and Company
Background on Non-Small Cell Lung Cancer Second Line	Frances Shepherd, M.D. Princess Margaret Hospital University of Toronto
Alimta Development	Roy Herbst, M.D., Ph.D. M.D. Anderson Cancer Center University of Texas
Clinical Efficacy from the Pivotal Study JMEI	Paul Bunn, M.D. University of Colorado Cancer Center
Safety Profile from the Pivotal Study JMEI	Richard Gralla, M.D. Multinational Association of Supportive Care in Cancer
Overall Conclusions	Paul Bunn, M.D.

FDA Presentation

Clinical Review	Martin H. Cohen, M.D., Medical Officer Division of Oncology Drug Products, FDA
Statistical Review	Yong-Cheng Wang, Ph.D., Statistical Reviewer, Division of Oncology Drug Products, FDA

Break

Open Public Hearing

Questions from the Committee

ODAC Discussion

The Committee issues were as follows:

Background

A randomized controlled unblinded trial was conducted in 571 patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy comparing Alimta with docetaxel. The primary objectives were 1) to show Alimta's superiority to docetaxel for overall survival and 2) to show Alimta's non-inferiority to docetaxel for overall survival if there was failure to show superiority. The efficacy results are summarized in the following Table.

	ITT ^a		RT ^b	
	Alimta	Docetaxel	Alimta	Docetaxel
Resp Rate (%) (95% CI)			9.1 (5.9, 13.2)	8.8 (5.7, 12.8)
P-val (Fisher) ^c			.999	
Resp Duration (median) ^d			4.6	5.3
PFS (median) ^d	2.9	2.9	2.9	3.0
HR (95% CI) p-val (Wald) ^c	.97 (.82,1.16) .759		.98 (.82,1.17) .821	
TTP (median) ^d	3.4	3.5	3.1	3.5
HR (95% CI) p-val (Wald) ^c	.97 (.80, 1.17) .721		1.01 (.83, 1.22) .951	
OS (median) ^d	8.3	7.9	8.4	8.0
HR (95% CI) p-val (log rank) ^c	.99 (.82, 1.20) .930		.97 (.80, 1.18) .765	

^aIntent to Treat

^bRandomized and Treated

^cAll p-values two-sided

^dMonths

The FDA believes Alimta non-inferiority for overall survival can not be demonstrated for two reasons. First, there is only one small historical study (total 104 patients) from which to estimate the survival effect of docetaxel, resulting in inability to estimate the docetaxel effect with precision, to evaluate interstudy variability and to assess constancy. A meta-analysis of multiple historical studies is ordinarily required for a non-inferiority analysis. Second, in the Alimta versus docetaxel study comparison of survival effect is confounded by the 32% crossover rate of Alimta patients to docetaxel after tumor progression and the greater number of docetaxel patients who did not receive any post study chemotherapy.

In the Alimta versus docetaxel study the Alimta 9.1% tumor response rate provides evidence of some Alimta anticancer activity and the similarity of Alimta and docetaxel in PFS and TTP provides some support for Alimta efficacy. If these were taken as surrogate effects reasonably likely to predict benefit and if Alimta had a documented safety advantage over docetaxel, accelerated approval could be a possibility.

Questions

1. Do you believe Alimta has a more favorable toxicity profile than docetaxel?

The committee agreed that although weight loss and neutropenia were, in fact, less on the Alimta arm than the docetaxel arm, both rash and nausea were present in the Alimta arm. One member noted however, that the increased dose of dexamethasone given in the docetaxel arm could account for lack of nausea and rash in this arm.

- *A vote was taken on this issue; the results are as follows:*

13	Yes
0	No

2. If the answer is yes, does the more favorable Alimta toxicity profile with supporting efficacy data on tumor response and PFS outweigh the uncertainty regarding loss of docetaxel survival effect by using Alimta? (Note: Question 2 was intended to obtain the committee's opinion on accelerated approval).

- *A vote was taken on this issue; the results are as follows:*

13	Yes
0	No

The following question was added during the meeting to address the committee's concerns of full approval. As noted during the discussion full approval is granted once the sponsor completes trials to confirm clinical benefit of the product. The sponsor made reference to several ongoing trials in this area, in which they expect to complete in the next 2-4 years.

3. Given the potential confounding effects of cross-over, and problems in estimating the control effect, is there a convincing effect on survival to warrant regular approval?

There was some additional discussion from the committee addressing the differences among accelerated and full approval, from a regulatory perspective. For verbatim comments, please refer to the transcript, which will be available in approximately 2 weeks.

- *A vote was taken on this issue; the results are as follows:*

8	No
5	Yes

The meeting was adjourned at approximately 1:30 p.m.

MEETING MINUTES

MEETING DATE: July 6, 2004

TIME: 11:00 am **LOCATION:** WOC2/rm 6002

NDA: 21-677

Meeting Request Submission Date: 6-29-04

Briefing Document Submission Date: 6-30-04

DRUG: Alimta® (pemetrexed)

SPONSOR/APPLICANT: Eli Lilly & Company

TYPE of MEETING:

1. Other – Statistics
2. **Proposed Indications (from briefing package):**
Second line Non-Small Cell Lung Cancer (NSCLC)

FDA PARTICIPANTS:

Grant Williams, M.D.	-- Deputy Director, Division of Oncology Drug Products
John Johnson, M.D.	-- Medical Team Leader
Martin Cohen, M.D.	-- Medical Reviewer
Rajeshwari Sridhara, Ph.D.	-- Acting Statistical Team Leader
Yong-Cheng Wang, Ph.D.	-- Statistical Reviewer
Peiling Yang, Ph.D.	-- Statistical Reviewer
Patty Garvey, R.Ph.	-- Project Manager
Robert O'Neill, Ph.D.	-- Director, Office of Biostatistics
Charles Anello, Sc.D.	-- Deputy Director, Office of Biostatistics
Kooros Mahjoob, Ph.D.	-- Acting Director, Division of Biometrics I
James Hung, Ph.D.	-- Acting Dep. Director, Division of Biometrics I
Aloka Chakravarthy, Ph.D.	-- Staff Director, Biologics and Therapeutics Statistical
Mark Rothmann, Ph.D.	-- Oncology Team Leader, Biologics and Therapeutics Statistical
Consultant: Ralph D'Agostino, Ph.D.	-- Professor of Mathematics/Statistics, Boston University

INDUSTRY PARTICIPANTS:

Paolo Paoletti, M.D.	-- Vice-President, Medical-Oncology
Edmundo Muniz, M.D.	-- Team Leader, Oncology Platform Team
Binh Nguyen, M.D., Ph.D.	-- Medical Director, Oncology Platform Team
William John, M.D.	-- Associate Medical Director, Oncology Platform Team
Sofia Paul, Ph.D.	-- Principal Research Scientist, Oncology Statistics
Patrick Peterson, Ph.D.	-- Principal Research Scientist, Oncology Statistics
Jennifer Stotka, M.D.	-- Executive Director, U.S. Regulatory Affairs
John Worzalla	-- Regulatory Research Scientist, US Regulatory Affairs
Consultants: Donald Berry, Ph.D.	-- University of Texas, M.D. Anderson Cancer Center
Scott Emerson, M.D., Ph.D.	-- University of Washington
via telephone: Anne E. White	-- Director, Project Management, Oncology Platform Team

MEETING OBJECTIVES (from briefing document):

1. Lilly seeks discussion on the sponsor's responses to the April 6 and May 7, 2004 FDA queries regarding statistical findings.
2. Lilly seeks FDA comments as to whether there are remaining statistical findings that require resolution.

BACKGROUND:

On April 6, 2004, the Division sent a facsimile to Lilly regarding the two non-inferiority tests and Lilly's calculation of the p value for the primary survival non-inferiority test in the Alimta registration trial. Lilly responded to the April 6, 2004 facsimile on April 14, 2004.

On May 7, 2004, the Division replied to Lilly's April 14, 2004 amendment. On June 4, 2004, the FDA and Lilly met to have further clarification and understanding of the May 7, 2004 facsimile.

During the June 4, 2004 meeting, the FDA agreed that Lilly would request a follow-up meeting and bring a consultant. This meeting is the follow-up meeting to allow FDA and Lilly to discuss their statistical positions.

DISCUSSION:

Prior to the meeting, Dr. Williams indicated that this was not a decision-making meeting. This meeting was to allow the FDA and Lilly to present their statistical positions prior to the ODAC meeting on July 27, 2004.

The meeting concluded at 12:45 p.m.

{See appended electronic signature page}

Patty Garvey, R.Ph.
Project Manager

Concurrence Chair:

{See appended electronic signature page}

Grant Williams, M.D.
Deputy Director, DODP

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

/s/

Grant Williams

7/30/04 09:39:26 AM

MEETING MINUTES

MEETING DATE: June 4, 2004

TIME: 10:00 am

LOCATION: WOC2/trm 3004

NDA: 21-677

Meeting Request & Briefing Document

Submission Date: 5-20-04

DRUG: Alimta® (pemetrexed)

SPONSOR/APPLICANT: Eli Lilly & Company

TYPE of MEETING:

1. Other - Statistics
2. **Proposed Indications (from briefing package):**
Second line Non-Small Cell Lung Cancer (NSCLC)

FDA PARTICIPANTS:

Richard Pazdur, M.D.	--	Director, Division of Oncology Drug Products (DODP)
John Johnson, M.D.	--	Medical Team Leader
Martin Cohen, M.D.	--	Medical Reviewer
Rajeshwari Sridhara, Ph.D.	--	Acting Statistical Team Leader
Yong-Cheng Wang, Ph.D.	--	Statistical Reviewer
Patty Garvey, R.Ph.	--	Project Manager

INDUSTRY PARTICIPANTS:

Paolo Paoletti, M.D.	--	Vice-President, Medical-Oncology
Edmundo Muniz, M.D.	--	Team Leader, Oncology Platform Team
Binh Nguyen, M.D., Ph.D.	--	Medical Director, Oncology Platform Team
Patrick Peterson, Ph.D.	--	Principal Research Scientist, Oncology Statistics
Sofia Paul, Ph.D.	--	Principal Research Scientist, Oncology Statistics
James Symanowski, Ph.D.	--	Research Advisor, Oncology Statistics
Debasish Roychowdhury, M.D.	--	Director, US Regulatory Affairs
via telephone: John Worzalla	--	Regulatory Research Scientist, US Regulatory Affairs

BACKGROUND:

On April 6, 2004, the Division sent a facsimile to Lilly requesting an adjustment procedure be employed to the two non-inferiority tests and information on Lilly's calculation of the p value for the primary survival non-inferiority test in the Alimta registration trial. Lilly responded to the April 6, 2004 facsimile on April 14, 2004.

On May 7, 2004, the Division replied to Lilly's April 14 amendment (attachment #1). Lilly has request this meeting for further clarification and understanding of the May 7, 2004 facsimile.

MEETING OBJECTIVES (from briefing document):

Lilly is seeking clarification to the Division's facsimile communication sent to Lilly on May 7, 2004 regarding non-inferiority analyses in the Alimta second line NSCLC registration trial (JMEI).

QUESTION for DISCUSSION with FDA RESPONSES and DECISIONS REACHED:

1. The sponsor requests clarification as to why the fraction retention analysis is considered by FDA to be a retrospective, exploratory analysis?

Discussion: The FDA explained that the analysis is considered retrospective and exploratory because the fraction retention was not pre-specified in the protocol.

The FDA was also concerned with the cross over and treatment effect in a non-inferiority trial. Since the control effect is difficult to estimate based on one small trial one must use a conservative estimate in the analysis.

2. In the FDA facsimile date May 7, 2004, the FDA stated the following in comment #1 "there is no multiplicity adjustment needed for JMEI survival tests." However, in 1(b) of the same facsimile the FDA wrote that "a multiplicity adjustment is definitely needed for the two different tests." The sponsor is not clear regarding the FDA concern based on these two differing statements and requests clarification.

*Discussion: FDA indicated that there are 2 non-inferiority analyses – fixed margin approach and fraction retention approach. When using the fixed margin hypothesis one does **not** need to use historical data however with the fraction retention one needs to use the historical data.*

Adjustment is necessary for 2 non-inferiority test. However, alpha adjustment for testing superiority and fixed margin hypothesis is not required.

3. The historical estimates from the TAX317 trial were known estimates prior to the JMEI trial, and given these historical estimates, the test for 50% retention is asymptotically equivalent to a test against a fixed margin (a mathematical result from the published paper by Rothmann et al. (Rothmann, M., Li, N., Chen, G., Chi, G.Y., Temple R. and Thou H.H., 2003, Design and Analysis of Non-Inferiority Mortality Trials in Oncology, Stat. Med. 22:239-64)). The sponsor requests further clarification why Lilly's April 14 explanation is unacceptable.

Discussion: FDA stated that when an active control size is being estimated from one single study and particularly small study as this (104 patients), then the FDA's approach is to use a conservative estimate rather than a point

estimate. An example of a conservative estimate would be to use a lower 95% confidence limit.

FDA indicated that a meta-analysis can not even be conducted because this is a one trial study and the p value would be too sensitive to the choice of estimate of control effect size.

FDA also reminded Lilly no consensus was reached regarding the estimate of control effect prior to the NDA submission.

4. The difference between FDA calculation and the sponsor calculation is that Lilly computed the value of $\ln(\text{HR})$ as the middle value of the 95% CI for $\ln(\text{HR})$. When inverted back to the HR scale, sponsor resulted in the same values of HR and the CI (see below) as described in the Taxotere label (versus inverting back via the FDA calculation which leads to an upper CI of 0.89. So the sponsor believes that their estimation of $\ln(\text{HR})$ and $\text{se}(\ln(\text{HR}))$ used in the percent retention analysis are precise. The sponsor seeks FDA comment regarding the two methods of calculation shown below.

FDA calculation

HR=.56
 95% CI for HR (.35, .88)

 95% CI for $\ln(\text{HR})$ (-1.0498, -.1278)
 $\ln \text{HR} = \ln(.56) = -.5798$
 $\text{Se}(\ln(\text{HR})) = (1.0498 - .1278) / (1.96 * 2) = .235$
 Note: $(-1.0498 - .1278) / 2 \neq -.5798$

Inverting back to the HR scale:
 $\text{HR} = \text{Exp}(\ln \text{HR}) = .56$
 $\text{Exp}\{(-.5798 - 1.96 * .235, -.5798 + 1.96 * .235)\}$
 $= \text{Exp}\{(-1.0404, -.1192)\}$
 $= (.35, .89)$

Sponsor calculation

95% CI for HR (.35, .88)

 95% CI for $\ln(\text{HR})$ (-1.0498, -.1278)
 $\ln(\text{HR}) = (-1.0498 - .1278) / 2 = -.5888$
 $\text{Se}(\ln(\text{HR})) = (1.0498 - .1278) / (1.96 * 2) = .235$

Inverting back to the HR scale:
 $\text{HR} = \text{Exp}\{\ln \text{HR}\} = .555$
 $\text{Exp}\{(-.5888 - 1.96 * .235, -.5888 + 1.96 * .235)\}$
 $= \text{Exp}\{-1.0498, -.1278\}$
 $= (.35, .88)$ as shown in the Taxotere_label

Discussion: Since this is a small study (104 patients), then the FDA approach is to use a conservative estimate rather than a point estimate. An example of a conservative estimate would be to use a lower 95% confidence limit.

FDA will check to see if they will be able to provide Lilly with the actual number the Taxotere application used for log HR and the standard of error of log HR.

ACTION ITEMS:

1. FDA will have further internal discussion regarding non-inferiority trial. This discussion will include using an outside consultant.

2. Lilly may request a follow-up meeting, for which Lilly may bring their consultant, after the FDA has more time to discuss internally.
3. FDA recommended that Lilly provide a briefing document for the follow-up meeting when it has been scheduled.
4. FDA will check to see if they will be able to provide Lilly with the actual number the Taxotere application used for log HR and the standard of error of log HR.

The meeting concluded at 11:15 a.m.

{See appended electronic signature page}

Patty Garvey, R.Ph.
Project Manager

Concurrence Chair:

{See appended electronic signature page}

Rajeshwari Sridhara, Ph.D.
Acting Statistical Reviewer

Attachment: FDA facsimile dated May 7, 2004



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-677

Eli Lilly & Company
Attention: John F. Worzalla
Regulatory Research Scientist, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Worzalla:

Please refer to your November 3, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alimta (pemetrexed, LY231514) for NSCLC.

We also refer to your submissions dated December 4, 10, and 23, 2003.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on January 3, 2004 in accordance with 21 CFR 314.101(a).

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

If you have any questions, call me as Patty is on leave for several weeks (301 594-5742).

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Dotti Pease

12/31/03 10:16:06 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-677

Eli Lilly & Company
Attention: John F. Worzalla
Regulatory Research Scientist, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Worzalla:

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: Alimta® (Pemetrexed, LY231514)
Review Priority Classification: Standard (S)
Date of Application: November 3, 2003
Date of Receipt: November 4, 2003
Our Reference Number: NDA 21-677

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 3, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 4, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room, 3067
5600 Fishers Lane
Rockville, Maryland 20857

NDA 21-677

Page 2

Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Oncology Drug Products, HFD-150

Attention: Document Room 3067

1451 Rockville Pike

Rockville, Maryland 20852

If you have any questions, call Patty Garvey, Regulatory Project Manager, at (301) 594-5766.

Sincerely,

{See appended electronic signature page}

Richard Pazdur

Director

Division of Oncology Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

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

/s/

Dotti Pease
12/19/03 12:45:30 PM
Signing for Richard Pazdur, M.D.

5 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

X § 552(b)(5) Deliberative Process



IND 40,061

Eli Lilly & Company
Attention: John F. Worzalla
Regulatory Research Scientist, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Worzalla:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for Alimta (pemetrexed, LY231514).

We also refer to your May 19, 2003, request for fast track designation submitted under section 506 of the Act.

We have reviewed your request and have concluded that it meets the criteria for fast track designation. Therefore, we are designating Alimta for locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy as a fast track product.

We are granting fast track designation for the following reasons:

1. Lung cancer is the leading cause of cancer death, accounting for over 150,000 deaths per year in the United States. The majority of patients with lung cancer have non-small cell cancer and most of these patients have locally advanced and metastatic disease.
2. A recently completed Phase 3 trial reports that Alimta had similar survival and an improved toxicity profile when compared to docetaxel in locally advanced and metastatic NSCLC patients with prior chemotherapy.

If you pursue a clinical development program that does not support use of Alimta for locally advanced or metastatic non-small cell lung cancer after prior chemotherapy, we will not review the application under the fast track development program.

IND 40,061

Page 2

If you have any questions, call Patty Garvey, Regulatory Project Manager, at 301-594-5766.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Richard Pazdur
7/23/03 10:55:44 AM

13 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

X _____ § 552(b)(5) Deliberative Process

29.1

DF

TELECON MINUTES

MEETING DATE: 9/27/00 **TIME:** 8:30A.M. **LOCATION:** WOC 2 Conf. Rm. B

IND: 40,061

Meeting Request Submission Date: September 27, 2000

DRUG: LY231514 Disodium

INDICATION: Tx. of locally advanced
metastatic Non- Small Cell Lung Cancer

SPONSOR/APPLICANT: Eli Lilly

TELECON: Non-inferiority questions

FDA PARTICIPANTS: HFD-150/Debra Vause, Project Manager
HFD-150/Gang Chen, Ph.D., Statistical Team Leader
HFD-150/Mark Rothmann, Ph.D., Statistician

INDUSTRY PARTICIPANTS: John Worzalla, Associate Regulatory Consultant
Dr. Clet Niyikiza, Ph.D., Research Scientist

MEETING OBJECTIVES: Non-inferiority questions

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

- Briefly discussed one FDA reviewed trial for historical literature related to the design of a non-inferiority trial
- FDA's concerns:
 1. Active control effect should be well established.
 2. Non-inferiority margin should be based on at least 50% retention of the control effect.
 3. Type I error under the non-inferiority test should be controlled at a one-sided 0.25 level.

ACTION ITEMS:

- FDA PM to send facsimile of log-hazard ratio estimate and associated standard error from FDA reviewed taxotere study, to sponsor
- Sponsor will submit a proposal for review by FDA statisticians of the non-inferiority trial

Debra Vause 10/3/00
Debra Vause, Project Manager

Chen Gang 10/2/00
Gang Chen, Ph.D., Statistical Team Leader

cc: Attendees electronically
HFD-150/D.Vause
HFD-150/G. Chen
HFD-150/M. Rothmann
HFD-150/Div. File

MEETING MINUTES

15 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

P § 552(b)(5) Deliberative Process

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-677	Efficacy Supplement Type SE-	Supplement Number
Drug: ALIMTA® (pemetrexed, LY231514)		Applicant: Eli Lilly & Company
RPM: Patty Garvey, R.Ph.	HFD-150	Phone # 301-594-05766
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	
❖ Application Classifications:		
<input type="checkbox"/> Review priority	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
<input type="checkbox"/> Chem class (NDAs only)	1	
<input type="checkbox"/> Other (e.g., orphan, OTC)	Not Applicable	
❖ User Fee Goal Dates		
		September 4, 2004
❖ Special programs (indicate all that apply)		
		<input type="checkbox"/> None Subpart H
		<input checked="" type="checkbox"/> 21 CFR 314.510 (accelerated approval)
		<input type="checkbox"/> 21 CFR 314.520 (restricted distribution)
		<input checked="" type="checkbox"/> Fast Track – Granted 7-23-03
		<input type="checkbox"/> Rolling Review
		<input type="checkbox"/> CMA Pilot 1
		<input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
<input type="checkbox"/> User Fee	<input checked="" type="checkbox"/> Paid	
<input type="checkbox"/> User Fee waiver	<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other	
<input type="checkbox"/> User Fee exception	<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other	
❖ Application Integrity Policy (AIP)		
<input type="checkbox"/> Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
<input type="checkbox"/> This application is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
<input type="checkbox"/> Exception for review (Center Director's memo)	Not Applicable	
<input type="checkbox"/> OC clearance for approval	Not Applicable	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.		
		<input checked="" type="checkbox"/> Verified
❖ Patent		
<input type="checkbox"/> Information: Verify that form FDA-3542a was submitted.	<input checked="" type="checkbox"/> Verified	
<input type="checkbox"/> Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)	
<input type="checkbox"/> For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	<input type="checkbox"/> Verified	

❖ Exclusivity (approvals only)	
• Exclusivity summary	August 19, 2004
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	N/A
General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	Not Applicable
• Status of advertising (approvals only)	() Materials requested in AP letter (X) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None () Press Release () Talk Paper () Dear Health Care Professional Letter (X) Other –FDA issued to ASCO, ONS and NCI burst emails
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Included in package
• Most recent applicant-proposed labeling	Not Applicable
• Original applicant-proposed labeling	November 3, 2003
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DDMAC review of PI – 8/3/04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Not Applicable
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Not Applicable
• Applicant proposed	Not Applicable
• Reviews	Not Applicable
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Included in package
• Documentation of discussions and/or agreements relating to post-marketing commitments	Included in package
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Included in package
❖ Memoranda and Telecons	Included in package
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	March 1, 2000; September 25, 1998 (clinical); and September 23, 1998 (biopharm – no minutes)
• Pre-NDA meeting (indicate date)	August 11, 2003 and May 15, 2003
• Pre-Approval Safety Conference (indicate date; approvals only)	Not Applicable

• Other	Included in package
❖ Advisory Committee Meeting	
• Date of Meeting	July 27, 2004
• 48-hour alert	Not Applicable
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	June 24, 2004
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	August 19, 2004
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	August 12, 2004
❖ Microbiology (efficacy) review(s) (indicate date for each review)	Not Applicable
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	August 12, 2004 – part of clinical review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	Not Applicable
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	April 22, 2004
❖ Statistical review(s) (indicate date for each review)	August 13, 2004
❖ Biopharmaceutical review(s) (indicate date for each review)	August 18, 2004
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	Not Applicable
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	August 9, 2004
• Bioequivalence studies	Not Applicable
CMC Information	
❖ CMC review(s) (indicate date for each review)	August 13, 2004
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	August 13, 2004 part of CMC review
• Review & FONSI (indicate date of review)	Not Applicable
• Review & Environmental Impact Statement (indicate date of each review)	Not Applicable
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	Not Applicable
❖ Facilities inspection (provide EER report)	Date completed: () Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	Not Applicable
❖ Nonclinical inspection review summary	Not Applicable
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	Not Applicable
❖ CAC/ECAC report	Not Applicable

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

/s/

Patricia Garvey
8/19/04 11:13:38 AM