

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-059**

**ADMINISTRATIVE**  
**DOCUMENTS/CORRESPONDENCE**

**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

22-059

NAME OF APPLICANT / NDA HOLDER

SmithKline Beecham Corporation (d.b.a.  
GlaxoSmithKline)

*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)

TYKERB®

ACTIVE INGREDIENT(S)

lapatinib ditosylate

STRENGTH(S)

250 mg/tablet

DOSAGE FORM

tablet

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 6,391,874	b. Issue Date of Patent 5/21/2002	c. Expiration Date of Patent 7/11/2017
d. Name of Patent Owner SmithKline Beecham (Cork) Limited	Address (of Patent Owner) Currabinny, Carrigaline	
	City/State County Cork	
	ZIP Code Ireland	FAX Number (if available) 011 44 20 8047 6894
	Telephone Number 011 44 20 8047 4455	E-Mail Address (if available) michael.a.reed@gsk.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)  ☞ SmithKline Beecham Corporation	Address (of agent or representative named in 1.e.) One Franklin Plaza PO Box 7929	
	City/State Philadelphia, Pennsylvania	
	ZIP Code 19101	FAX Number (if available) 919-483-7988
	Telephone Number 919-483-8247	E-Mail Address (if available) john.l.lemanowicz@gsk.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? <input type="checkbox"/> Yes <input type="checkbox"/> 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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> 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?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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).	<input type="checkbox"/> Yes	<input type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**3. 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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No

**4. Method of Use (Section 4 is continued on page 4 of this Form)**

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?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 30	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.) TYKERB®, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2)	

**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.  Yes

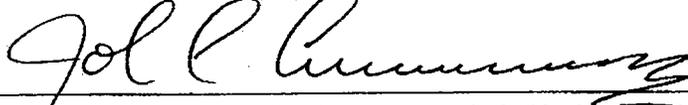
**6. Declaration Certification**

**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**



7/31/06

**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**

John L. Lemanowicz, Senior Patent Counsel, GlaxoSmithKline

**Address**

Five Moore Drive

**City/State**

Research Triangle Park, NC

**ZIP Code**

27709-3398

**Telephone Number**

919-483-8247

**FAX Number (if available)**

919-483-7988

**E-Mail Address (if available)**

John.l.lemanowicz@gsk.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

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**4. Method of Use (continued)**

**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) 31 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.)  
TYKERB®, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2)

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Composition) and/or Method of Use*

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**1. GENERAL**

a. United States Patent Number

6,713,485

b. Issue Date of Patent

3/30/2004

c. Expiration Date of Patent

1/8/2019

d. Name of Patent Owner

SmithKline Beecham (Cork) Limited

Address (of Patent Owner)

Currabinny, Carrigaline

City/State

County Cork

ZIP Code

Ireland

FAX Number (if available)

011 44 20 8047 6894

Telephone Number

011 44 20 8047 4455

E-Mail Address (if available)

michael.a.reed@gsk.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)

SmithKline Beecham Corporation

Address (of agent or representative named in 1.e.)

One Franklin Plaza

PO Box 7929

City/State

Philadelphia, Pennsylvania

ZIP Code

19101

FAX Number (if available)

919-483-7988

Telephone Number

919-483-8247

E-Mail Address (if available)

john.l.lemanowicz@gsk.com

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

**3. 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 (Section 4 is continued on page 4 of this Form)**

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4.2 Patent Claim Number (as listed in the patent) 3 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.)  
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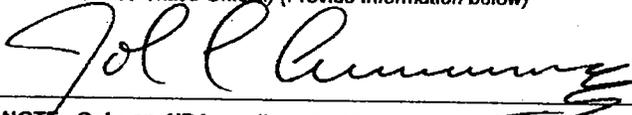
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7/31/06

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Patent Owner

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

Name

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Telephone Number

919-483-8247

FAX Number (if available)

919-483-7988

E-Mail Address (if available)

john.l.lemanowicz@gsk.com

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**4. Method of Use (continued)**

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**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) **4** 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.)  
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**PATENT INFORMATION SUBMITTED WITH THE  
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**1. GENERAL**

a. United States Patent Number

6,727,256

b. Issue Date of Patent

4/27/2004

c. Expiration Date of Patent

1/8/2019

d. Name of Patent Owner

SmithKline Beecham (Cork) Limited

Address (of Patent Owner)

Currabinny, Carrigaline

City/State

County Cork

ZIP Code

Ireland

FAX Number (if available)

011 44 20 8047 6894

Telephone Number

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micha.l.a.reed@gsk.com

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**3. 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 (Section 4 is continued on page 4 of this Form)**

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) **5** 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.)  
**TYKERB®, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2)**

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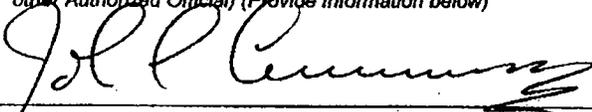
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**4. Method of Use (continued)**

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4.2 Patent Claim Number (as listed in the patent) 6 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.)

TYKERB®, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2);

**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

22-059

NAME OF APPLICANT / NDA HOLDER

SmithKline Beecham Corporation (d.b.a.  
GlaxoSmithKline)

*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)

TYKERB®

ACTIVE INGREDIENT(S)

lapatinib ditosylate

STRENGTH(S)

250 mg/tablet

DOSAGE FORM

tablet

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

6,828,320

b. Issue Date of Patent

12/7/2004

c. Expiration Date of Patent

7/11/2017

d. Name of Patent Owner

SmithKline Beecham (Cork) Limited

Address (of Patent Owner)

Currabinny, Carrigaline

City/State

County Cork

ZIP Code

Ireland

FAX Number (if available)

011 44 20 8047 6894

Telephone Number

011 44 20 8047 4455

E-Mail Address (if available)

michael.a.reed@gsk.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)

SmithKline Beecham Corporation

Address (of agent or representative named in 1.e.)

One Franklin Plaza

PO Box 7929

City/State

Philadelphia, Pennsylvania

ZIP Code

19101

FAX Number (if available)

919-483-7988

Telephone Number

919-483-8247

E-Mail Address (if available)

john.l.lemanowicz@gsk.com

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

**3. 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 (Section 4 is continued on page 4 of this Form)**

**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) 1 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.)  
 TYKERB®, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2);

**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.  Yes

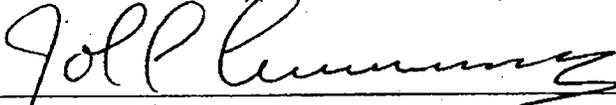
6. Declaration Certification

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



7/31/06

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

John L. Lemanowicz, Senior Patent Counsel, GlaxoSmithKline

Address

Five Moore Drive

City/State

Research Triangle Park, NC

ZIP Code

27709-3398

Telephone Number

919-483-8247

FAX Number (if available)

919-483-7988

E-Mail Address (if available)

John.l.lemanowicz@gsk.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.

**4. Method of Use (continued)**

**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) **2** 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.)  
TYKERB®, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2)

February 6, 2007



GlaxoSmithKline

Robert Justice, M.D., Director  
Division of Drug Oncology Products  
Center for Drug Evaluation and Research  
Attn: Document Control Room  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**GlaxoSmithKline**  
2301 Renaissance Boulevard  
P.O. Box 61540  
King of Prussia, PA  
19406-2772  
Tel. 610 787 7000  
Fax. 610 787 7777  
www.gsk.com

**Re: NDA 22-059; Tykerb® (lapatinib ditosylate) Tablets  
Amendment to Pending Application: Patent Information**

Dear Dr. Justice:

Reference is made to our pending NDA 22-059 for Tykerb® (lapatinib) tablets that was submitted to FDA on 13 September 2006. *Tykerb*, in combination with capecitabine, is targeted for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2)

— Also, please refer to our submission of 1 February 2007 adding an additional patent to our application in Module 1.3.5.1 of the NDA.

Please note there were several typographical errors in that patent submission of 1 February 2007, and GlaxoSmithKline (GSK) wishes to replace that submission with the current document. GSK regrets any inconvenience this may cause the Division.

If you have any questions, please call me at (610) 787-3724; I can be reached by fax at (610) 787-7062.

Sincerely,

A handwritten signature in black ink, appearing to read "Richard Swenson".

Richard Swenson, Ph.D.  
Senior Director  
Regulatory Affairs

Trade secret and/or confidential commercial information contained in this submission is exempt from public disclosure to the full extent provided under law.

# **GUIDE TO FDA REVIEWERS**

## **1. ELECTRONIC SUBMISSION**

All documents included in this submission are provided as electronic files in Portable Document Format (PDF). The submission has been organized into a folder-based structure in compliance with the guidance for Providing Regulatory Submissions in Electronic Format (IT3 January 1999).

### **1.1. CTD Hybrid Format**

The components of this submission are provided in CTD format in accordance with the FDA draft guidance "Submitting Marketing Applications According to the ICH-CTD Format - General Considerations" (August 2001) and "FDA eCTD Table of Contents Headings and Hierarchy" (July 7, 2005)

## **2. ELECTRONIC DESCRIPTION**

Contents of the media: one (1) transmission through the Electronic Submission Gateway (ESG).

Total size of the submission: Approx. .5 mb

## **3. VIRUS VERIFICATION**

This submission is virus-free and confirmed via Symantec AntiVirus Corporate Edition v8.00.9374 (4.1.0.15).

**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

22-059

NAME OF APPLICANT / NDA HOLDER

SmithKline Beecham Corporation (d.b.a.  
GlaxoSmithKline)

*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)  
TYKERB®

ACTIVE INGREDIENT(S)  
lapatinib ditosylate

STRENGTH(S)  
250 mg/tablet

DOSAGE FORM  
tablet

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  
7,157,466

b. Issue Date of Patent  
1/2/2007

c. Expiration Date of Patent  
11/19/2021

d. Name of Patent Owner  
SmithKline Beecham (Cork) Limited

Address (of Patent Owner)  
Currabinny, Carrigaline

City/State  
County Cork

ZIP Code  
Ireland

FAX Number (if available)  
011 44 20 8047 6894

Telephone Number  
011 44 20 8047 4455

E-Mail Address (if available)  
michael.a.reed@gsk.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.)

One Franklin Plaza  
PO Box 7929

City/State  
Philadelphia, Pennsylvania

ZIP Code  
19101

FAX Number (if available)  
919-483-7988

Telephone Number  
919-483-8247

E-Mail Address (if available)  
john.l.lemanowicz@gsk.com

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

**3. 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 the 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

*John L. Lemanowicz*

2/6/07

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

John L. Lemanowicz, Senior Patent Counsel, GlaxoSmithKline

Address

Five Moore Drive

City/State

Research Triangle Park, NC

ZIP Code

27709-3398

Telephone Number

919-483-8247

FAX Number (if available)

919-483-7988

E-Mail Address (if available)

john.l.lemanowicz@gsk.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.

## EXCLUSIVITY SUMMARY

NDA # 22-059

SUPPL #

HFD # 150

Trade Name TYKERB (lapatinib) tablets

Generic Name

Applicant Name SmithKline Beecham Corporation, d/b/a GlaxoSmithKline

Approval Date, If Known March 13, 2007

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES

NO

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

505(b)(1)

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

YES

NO

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

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

N/A

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

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

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

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

### 1. Single active ingredient product.

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

YES  NO

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

NDA#

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

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

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

summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1

YES

NO

Investigation #2

YES

NO

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

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

Investigation #1

YES

NO

Investigation #2

YES

NO



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

If yes, explain:

---

Name of person completing form: Kim J. Robertson  
Title: Consumer Safety Officer  
Date: February 16, 2007

Name of Office/Division Director signing form: Robert L. Justice, M.D.  
Title: Division Director, Division of Drug Oncology Products

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

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

/s/

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Robert Justice  
3/13/2007 03:07:12 PM

**PEDIATRIC PAGE**

(Complete for all filed original applications and efficacy supplements)

MA/BLA #: NDA 22-059 Supplement Type (e.g. SE5): N/A Supplement Number: 000

Stamp Date: September 13, 2006 PDUFA Goal Date: March 13, 2007

HFD -150 Trade and generic names/dosage form: TYKERB® (lapatinib) tablets 250 mg

Applicant: GlaxoSmithKline Therapeutic Class: 5010410

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? \*

- Yes. Please proceed to the next question.
- No. PREA does not apply. Skip to signature block.

\* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): NONE

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: TYKERB, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumors over-express HER2 (ErbB2) and who have received prior therapy including an anthracycline, a taxane and trastuzumab.

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

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 (fill in applicable criteria below):

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 (fill in applicable criteria below):

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 (fill in applicable criteria below):

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: **Kim J. Robertson**

*{See appended electronic signature page}*

**Consumer Safety Officer**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

**(Revised: 10/10/2006)**

*[Faint, illegible text and markings, possibly bleed-through or scanning artifacts]*

**Attachment A**

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

Indication #2: \_\_\_\_\_

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

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 (fill in applicable criteria below):

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*

plete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred (fill in applicable criteria below)::

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 (fill in applicable criteria below):

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

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

**REQUEST FOR FULLWAIVER OF  
PEDIATRIC USE STUDIES**

1.9.1 Request Waiver Pediatric Studies

**MODULE 1.9.1 – REQUEST FOR FULL WAIVER OF PEDIATRIC USE STUDIES**

The proposed indication for TYKERB (lapatinib ditosylate) Tablets, in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2) and who have received prior therapy including trastuzumab.

In accordance with 505(B)(a)(4)(A)(i) of the Federal Food, Drug, and Cosmetic Act, GlaxoSmithKline (GSK) believes that necessary studies are impossible or highly impractical to conduct with TYKERB in pediatric patients because of the very small number of potential with advanced or metastatic breast cancer.

The proposed indication for TYKERB is for an indication that has extremely limited applicability to pediatric patients because the pathophysiology of this disease occurs, for the most part, in the adult population. As noted in Attachment A of the FDA Guidance “How to Comply with the Pediatric Research Equity Act”, **breast cancer qualifies for a “disease-specific” waiver.**

Therefore, in accordance with 21 CFR §314.55(c)(2)(ii), the applicant hereby respectfully requests that FDA grant a full waiver of the requirements of paragraph (a) of 21 CFR §314.55.

NDA 22-059  
NDA for Tykerb (lapatinib ditosylate) Tablets  
Treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2  
(ErbB2)

DEBARMENT CERTIFICATION

GlaxoSmithKline hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Charles E. Mueller or Mertie V. Snead  
Director, North America Clinical Compliance  
Worldwide Regulatory Compliance

25 Jul 2004

Date

## ACTION PACKAGE CHECKLIST

Application Information		
NDA # 22-059	NDA Supplement # N/A	If NDA, Efficacy Supplement Type
Proprietary Name: TYKERB® (lapatinb) tablets, 250 mg Established Name: (lapatinib) Dosage Form: 250 mg		Applicant: GlaxoSmithKline
RPM: Kim J. Robertson		Division: HFD-150      Phone # (301) 796-2330
NDAs: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		Provide a brief explanation of how this product is different from the listed drug.  <input type="checkbox"/> If no listed drug, check here and explain:
❖ User Fee Goal Date: <b>March 13, 2007</b> ❖ Action Goal Date (if different): <b>March 13, 2007</b>		
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None
❖ Advertising ( <i>approvals only</i> ) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed ( <i>indicate dates of reviews</i> )		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): 1	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2  <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug  Other:  Other comments:	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP                             <ul style="list-style-type: none"> <li>Exception for review (<i>file Center Director's memo in Administrative Documents section</i>)</li> <li>OC clearance for approval (<i>file communication in Administrative Documents section</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<p>❖ <b>Exclusivity</b></p>	
<ul style="list-style-type: none"> <li>• NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>)</li> </ul>	<p>X Included</p>
<ul style="list-style-type: none"> <li>• Is approval of this application blocked by any type of exclusivity?             <ul style="list-style-type: none"> <li>• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> <li>• NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> <li>• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> <li>• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul> </li> </ul>	<p>X No      <input type="checkbox"/> Yes</p> <p>X No      <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:</p> <p>X No      <input type="checkbox"/> Yes If, yes, NDA #      and date exclusivity expires:</p> <p>X No      <input type="checkbox"/> Yes If, yes, NDA #      and date exclusivity expires:</p> <p>X No      <input type="checkbox"/> Yes If, yes, NDA #      and date exclusivity expires:</p>
<p>❖ <b>Patent Information (NDAs and NDA supplements only)</b></p>	
<ul style="list-style-type: none"> <li>• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<p>X Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.</p>
<ul style="list-style-type: none"> <li>• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> <li>• [505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<p>21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified</p> <p>21 CFR 314.50(i)(1) <input type="checkbox"/> (ii)    <input type="checkbox"/> (iii)</p> <p><input type="checkbox"/> No paragraph III certification Date patent will expire</p>
<ul style="list-style-type: none"> <li>• [505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i></li> <li>• [505(b)(2) applications] For <b>each paragraph IV</b> certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</li> </ul> <p>Answer the following questions for <b>each</b> paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified</p> <p><input type="checkbox"/> Yes      <input type="checkbox"/> No</p>

notice of certification?

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

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

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

Yes  No

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

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

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

Yes  No

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

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

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

Yes  No

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

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
<b>Summary Reviews</b>	
❖ Summary Reviews (e.g., Office Director, Division Director) <i>(indicate date for each review)</i>	Division Dir. March 6, 2007
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) <i>(indicate date)</i>	
<b>Labeling</b>	
❖ Package Insert	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	March 7, 2007
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	March 5, 2007
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	September 13, 2006
❖ Patient Package Insert	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	March 7, 2007
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	March 5, 2007
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	September 13, 2006
❖ Medication Guide	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	
❖ Labels ( <b>full color</b> carton and immediate-container labels)	
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labels (only if generated after latest applicant submission)</li> </ul>	December 6, 2006
<ul style="list-style-type: none"> <li>• Most recent applicant-proposed labeling</li> </ul>	March 7, 2007

❖ Labeling reviews and minutes of any labeling meetings ( <i>indicate dates of reviews and meetings</i> )	X DMETS November 17, 2006 X DSRCS March 8, 2007 X DDMAC October 20, 2006 X SEALD December 19, 2006 X <b>Other reviews:</b> DSI/December 19, 2006, QT/December 15, 2006, Labeling & Nomenclature/December 19, 2006 <input type="checkbox"/> Memos of Mtgs
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Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) ( <i>indicate date of each review</i> )	PM Filing Review March 8, 2007
❖ NDA and NDA supplement approvals only: Exclusivity Summary ( <i>signed by Division Director</i> )	X Included
❖ AIP-related documents <ul style="list-style-type: none"> <li>Center Director's Exception for Review memo</li> <li>If AP: OC clearance for approval</li> </ul>	N/A
❖ Pediatric Page (all actions)	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. ( <i>Include certification.</i> )	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>)</li> </ul>	March 2, 2007
<ul style="list-style-type: none"> <li>Incoming submission documenting commitment</li> </ul>	March 07, 2007
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Numerous dates in Correspondence Tab
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> </ul>	March 6, 2007
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> No mtg December 22, 2006
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date</i>)</li> </ul>	<input type="checkbox"/> No mtg July 8, 2003
<ul style="list-style-type: none"> <li>Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	CMC Pilot Mtgs. : June 16, 2006
❖ Advisory Committee Meeting	X No AC meeting
<ul style="list-style-type: none"> <li>Date of Meeting</li> <li>48-hour alert or minutes, if available</li> </ul>	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) ( <i>indicate date for each review</i> )	December 15 & 18, 2006
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> <li>X Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)</li> </ul>	December 15, 2006
<ul style="list-style-type: none"> <li><input type="checkbox"/> Review &amp; FONSI (<i>indicate date of review</i>)</li> </ul>	

<ul style="list-style-type: none"> <li>• <input type="checkbox"/> Review &amp; Environmental Impact Statement (<i>indicate date of each review</i>)</li> </ul>	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) ( <i>indicate date of each review</i> )	<input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: September 29, 2006 X Acceptable <input type="checkbox"/> Withhold recommendation

<ul style="list-style-type: none"> <li>❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> <li>• Facility review (<i>indicate date(s)</i>)</li> <li>• Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	X Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
<b>Nonclinical Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	March 5, 2007
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	X None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	X No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	X None requested
<b>Clinical Information</b>	
❖ Clinical review(s) ( <i>indicate date for each review</i> )	March 6, 2007
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	Page 24 of Medical Officer Review
❖ Clinical consult reviews from other review disciplines/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None DCRP (QT Study Report) December 15, 2006; DMIHP Review-December 18, 2006
❖ Microbiology (efficacy) reviews(s) ( <i>indicate date of each review</i> )	X Not needed
❖ Safety Update review(s) ( <i>indicate location/date if incorporated into another review</i> )	March 6, 2007
❖ Risk Management Plan review(s) (including those by OSE) ( <i>indicate location/date if incorporated into another review</i> )	March 9, 2007
❖ Controlled Substance Staff review(s) and recommendation for scheduling ( <i>indicate date of each review</i> )	X Not needed
❖ DSI Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested
<ul style="list-style-type: none"> <li>• Clinical Studies</li> <li>• Bioequivalence Studies</li> <li>• Clin Pharm Studies</li> </ul>	December 19 (2), 2006, January 12, 2007 & February 13, 2007
❖ Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None March 2, 2007
❖ Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None February 27, 2007

## Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 22-059 Supplement # N/A Efficacy Supplement Type SE- N/A

Proprietary Name: **TYKERB® (lapatinib) tablets**  
Established Name: **(lapatinib)**  
Strengths: **250 mg**

Applicant: **GSK**  
Agent for Applicant (if applicable): **N/A**

Date of Application: **September 13, 2006**  
Date of Receipt: **September 13, 2006**  
Date clock started after UN: **N/A**  
Date of Filing Meeting: **October 17, 2006**  
Filing Date: **November 12, 2006**  
Action Goal Date (optional): **December 15, 2006**

User Fee Goal Date: **March 13, 2007**

Indication(s) requested: **Tykerb, in combination with capecitabine, is for the treatment of patients with advanced or metastatic breast cancer whose tumors over-express HER2 (ErbB2)**

Type of Original NDA: (b)(1)  (b)(2)   
AND (if applicable)  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S  P   
Resubmission after withdrawal?  Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.) 1  
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

User Fee Status: Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application.*

*Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES  NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES  NO

- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:

- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES  NO

2. This application is an eNDA or combined paper + eNDA YES

This application is: All electronic  Combined paper + eNDA

This application is in: NDA format  CTD format

Combined NDA and CTD formats

Does the eNDA, follow the guidance?

(<http://www.fda.gov/cder/guidance/2353fml.pdf>)

YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments: N/A

3. This application is an eCTD NDA. YES  NO

**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments: N/A

- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, X- Years NO   
5yrs

*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES X NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES X NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO
- Is this submission a partial or complete response to a pediatric Written Request? YES  NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**

*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO
- PDUFA and Action Goal dates correct in tracking system? YES X NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 61,362
- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO  
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) July 8, 2003 NO

If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) December 22, 2006 NO   
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) November 21, 2003 NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES  NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES  NO   
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES  NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A  YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA  YES  NO

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO

- If EA submitted, consulted to EA officer, OPS? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team? YES  NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 7, 2007

NDA #: 22-059

DRUG NAMES: TYKERB® (lapatinb) tablets, 250 mg

APPLICANT: GlaxoSmithKline

BACKGROUND: GlaxoSmithKline has submitted an NDA for TYKERB®, a kinase inhibitor professing to be designed to target ErbB1 and ErbB2 receptors that are frequently over-expressed in human cancers. (Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES:

ASSIGNED REVIEWERS (including those not present at filing meeting): See Below↓

**Discipline/Organization**

**Reviewer**

Medical:	Qin Ryan, M.D., Ph.D.
Secondary Medical:	Amna Ibrahim, M.D.
Statistical:	Chia-wen (Kiki) Ko, Ph.D.
Pharmacology:	Kimberly Benson, Ph.D
Statistical Pharmacology:	N/A
Chemistry:	X. Chen, Ph.D., C. Bertha, Ph.D., T. Ocheltree, Ph.D
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Gene Williams, Ph.D., Roshni Ramchandani, Ph.D.
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Lauren Iacono-Connor, Ph.D, Leslie Ball, M.D.
OPS:	N/A
Regulatory Project Management:	Kim J. Robertson, CSO
Other Consults:	DMETS, SEALD, QT, DDMAC, DSI, DSRCS, DMIHP, Labeling & Nomenclature

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

If no, explain: N/A

CLINICAL FILE  REFUSE TO FILE

- Clinical site audit(s) needed? YES  NO   
If no, explain:
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

	N/A	X	YES	<input type="checkbox"/>	NO	<input type="checkbox"/>
CLINICAL MICROBIOLOGY	N/A	X	FILE	<input type="checkbox"/>	REFUSE TO FILE	<input type="checkbox"/>
STATISTICS	N/A	<input type="checkbox"/>	FILE	X	REFUSE TO FILE	<input type="checkbox"/>
BIOPHARMACEUTICS			FILE	X	REFUSE TO FILE	<input type="checkbox"/>
					<input type="checkbox"/>	NO X
• Biopharm. study site audits(s) needed? YES						
PHARMACOLOGY/TOX	N/A	<input type="checkbox"/>	FILE	X	REFUSE TO FILE	<input type="checkbox"/>
• GLP audit needed?					YES <input type="checkbox"/>	NO X
CHEMISTRY			FILE	X	REFUSE TO FILE	<input type="checkbox"/>
• Establishment(s) ready for inspection?					YES X	NO <input type="checkbox"/>
• Sterile product?					YES <input type="checkbox"/>	NO X
• If yes, was microbiology consulted for validation of sterilization?					YES <input type="checkbox"/>	NO <input type="checkbox"/>

**ELECTRONIC SUBMISSION:**

Any comments: N/A

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
  - No filing issues have been identified.
  - X Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1.  Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. X Convey document filing issues/no filing issues to applicant by Day 74.

Kim J. Robertson  
Consumer Safety Officer

In this filing review, the following deficiencies/issues have been identified:

1. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

The applicant should propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or rationale why pharmacologic class should be omitted from the Highlights.

2. Cross referencing is incorrect throughout the labeling.
3. Subheading 8.6 of the Full Prescribing Information: Contents refers to an incorrect reference.
4. The dashes for dosage strengths should be removed.
5. — should be referred to as “Adverse Reactions” throughout the label.
6. — should be removed from the label.

## Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES  NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES  NO

*If "Yes," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES  NO

*If "Yes" contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES  NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," to (a) skip to question 6. Otherwise, answer part (b) and (c).*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES  NO

*If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO

*If "Yes," to (c), proceed to question 7.*

*NOTE: If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES  NO

*If "No," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES  NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES  NO

11. Is the application for a duplicate of a listed drug whose only difference is YES  NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))?  
If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? YES  NO   
(This is different from the patent declaration submitted on form FDA 3542 and 3542a.)

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

Not applicable (e.g., solely based on published literature. See question # 7

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s):

**NOTE:** IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must *subsequently* submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):

Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES  NO

*If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*

*Was this listed drug product(s) referenced by the applicant? (see question # 2)*

YES  NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A  YES  NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES  NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

# REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

## Division of Drug Oncology Products

Application Number: NDA 22-059

Name of Drug: TYKERB® (lapatinib) tablets, 250 mg

Applicant: GlaxoSmithKline

### Material Reviewed:

Submission Date(s): September 13, 2006

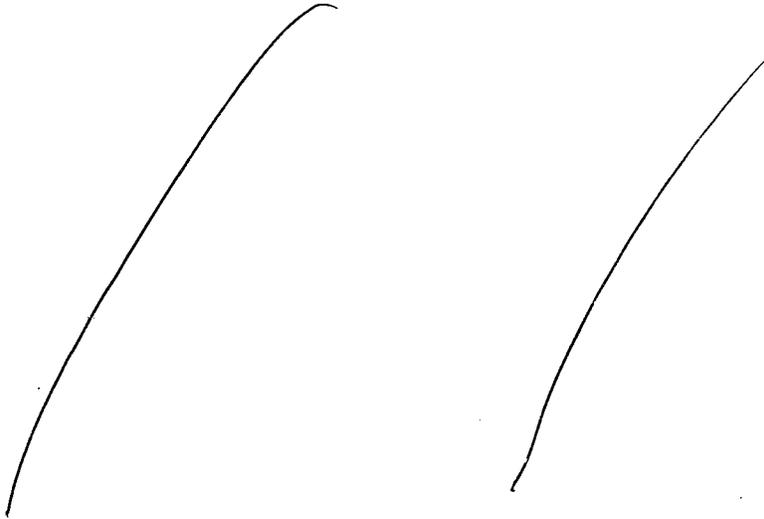
Receipt Date(s): September 13, 2006

Submission Date of Structure Product Labeling (SPL): October 30, 2006

Type of Labeling Reviewed: WORD

### Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.



**Recommendations**

Convey to applicant above deficiencies/issues in 74 day letter.

**Subsequent to issuance of 74 day letter:**

GlaxoSmithKline addressed the identified deficiencies/issues and re-submitted labeling on October 30, 2006.

I reviewed the October 30, 2006, resubmitted labeling and noted the inserted revisions as stated by the applicant. No additional issues/deficiencies were noted.

\_\_\_\_\_  
Kim J. Robertson  
Consumer Safety Officer

Supervisory Comment/Concurrence:

\_\_\_\_\_  
Frank Cross, Jr.  
Chief, Project Management Staff

Drafted: KJR/March 7, 2007  
Revised/Initialed: fhc/3.8.07  
Finalized: FCross/ March 8, 2007  
Filename: C:\cso\Robertson\NDA's\22059\PM Labeling Review  
**CSO LABELING REVIEW OF PLR FORMAT**

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/s/

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Kim Robertson  
3/8/2007 06:48:13 PM  
CSO  
PM/PLR Review NDA 22-059

Frank Cross  
3/9/2007 12:13:13 PM  
CSO

March 7, 2007



Robert Justice, M.D., Director  
Division of Drug Oncology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**GlaxoSmithKline**  
2301 Renaissance Boulevard  
P.O. Box 61540  
King of Prussia, PA  
19406-2772  
Tel. 610 787 7000  
Fax. 610 787 7777  
www.gsk.com

**Re: NDA 22-059; Tykerb® (Lapatinib)Tablets**  
**Response to FDA Request/Comment: Post Marketing Commitments**

Dear Dr. Justice:

Reference is made to our pending NDA 22-059 for Tykerb® (lapatinib) tablets. Also, please refer to an Email from Ms. Kim Robertson dated 2 March 2007 providing FDA-revisions to proposed labeling for *Tykerb* and a statement of proposed Post Marketing Commitments.

GlaxoSmithKline (GSK) has filled out the dates that were left blank in the FDA document (Attachment 1). This response also was sent to FDA via Email to Ms. Kim Robertson today.

If you have any questions, please call me at (610) 787-3724; I can be reached by fax at (610) 787-7062.

Sincerely,

A handwritten signature in black ink, appearing to read "Richard Swenson".

Richard Swenson, Ph.D.  
Senior Director  
Regulatory Affairs

Trade secret and/or confidential commercial information contained in this submission is exempt from public disclosure to the full extent provided under law.

A

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       Deliberative Process



**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

---

**DATE:** March 7, 2007

**TO:** Robert Justice, M.D., Director  
Division of Oncology Drug Products (DODP), HFD-150

**THROUGH:** Ellis Unger, MD, Acting Deputy Director  
Office of Surveillance and Epidemiology (OSE)

**FROM:** OSE Risk Management Team

**DRUG:** Tykerb® (Lapatinib)

**NDA #:** 22-059

**SPONSOR:** GSK

**SUBJECT:** Review of Proposed Risk Management Plan submitted August 26, 2006.

**RCM#:** 2007-412

**INTRODUCTION/BACKGROUND**

This review follows a request from the Division of Drug Oncology Products (DDOP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed Risk Management Plan (RMP) for Tykerb® (lapatinib) submitted August 25, 2006.

Tykerb® (lapatinib) is an orally administered, small-molecule, reversible, tyrosine kinase inhibitor (TKI) that targets both ErbB1 and ErbB2 receptors. ErbB1 and ErbB2 receptors frequently overexpress or are altered in human cancers, and ErbB2 positive cancers tend to be more aggressive and associated with a greater risk for disease progression and death. It is hypothesized that a compound that inhibits both ErbB1 and ErbB2 should have significant therapeutic advantages over compounds that inhibit only one of the receptors.

The proposed indication of Tykerb® (Lapatinib), in combination with capecitabine, is for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2)

The Sponsor's safety database includes approximately 3,100 subjects that received lapatinib in combination or as monotherapy as of the clinical cut-off date. The Sponsor examined toxicities known to be associated with inhibition of ErbB1 and ErbB2 receptors. These include diarrhea, rash, decreased left ventricular ejection fraction (LVEF) and pneumonitis. The Sponsor's Clinical Overview states that overall the most common adverse events observed in the lapatinib clinical studies were diarrhea, palmar-plantar erythrodysesthesia (an event common with capecitabine alone), nausea, rash, and fatigue. Lapatinib in combination with capecitabine was associated with similar toxicities as would be seen with each single agent, except in one study (Study EGF100151) where more subjects in the lapatinib plus capecitabine group (98 of 164 subjects; 60%) had diarrhea than in the capecitabine group (60 of 152 subjects; 39%).

The cardiac safety experience to date shows a limited number of cases of decreased LVEF, which are largely asymptomatic and reversible. Across the entire lapatinib program subjects (including subjects on control arms) experienced 63 events of decreased LVEF. Of these 63 events, 57 events (55 subjects) met the protocol specific serious definition included in the lapatinib Phase II and III protocols. Forty-one (41) of the 55 subjects whose LVEF decrease met the protocol-specific definition of serious are known to have received lapatinib, giving an incidence of 1.3% (out of 3,147 subjects). Across the entire lapatinib clinical program, pulmonary events have been reported for 9 subjects (5 experienced interstitial lung disease and 4 experienced pneumonitis). The majority of these reports were complicated by pre-existing conditions or previous/concurrent medications. No overall differences in safety of the combination of lapatinib and capecitabine or single agent lapatinib were observed between subjects 65 years and older versus younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.<sup>1</sup>

Based on the safety analysis of one controlled study of 399 patients (198 in testing arm and 201 in control arm) by the Medical Officer, Dr. Qin Ryan, it appears that the observed risks of decreased LVEF as well as the gastrointestinal and dermatologic adverse events are common among the studied cancer patients and consistent with other cancer therapies. Even though the incidence of LVEF was low (less than 2%), and in most cases was reversible, it is possible that the incidence of LVEF was under represented in this study, as is not uncommon with drugs when studied in relatively small numbers of patients. Therefore, monitoring of LVEF has been included in the lapatinib label in the WARNING AND PRECAUTIONS section. This patient population may be at greater risk because of prior administration of cardiotoxic drugs such as anthracycline and trastuzumab therapy.

<sup>1</sup> Original NDA 22-059 submitted Aug.25, 2006; Module 2.5 Clinical Overview

The sponsor does not believe that a Risk Minimization Action Plan (RiskMAP) is warranted for this product because the adverse events are expected and consistent with other cancer therapies. With regard to the potential and known risks, the Sponsor proposes to utilize labeling and routine post-marketing pharmacovigilance as risk management measures for Lapatinib. Each risk and proposed risk minimization and pharmacovigilance activity is described below.

#### Potential Risks

- Decreased LVEF  
Ejection fraction decreases is included in the proposed labeling. The sponsor proposes to monitor this event via routine postmarketing safety reporting requirements to ensure that the label adequately describes cardiac risks associated with Lapatinib.
- Pneumonitis  
The Sponsor does not propose to include this information in the labeling; however, will monitor this event via routine postmarketing safety reporting requirements.
- Diarrhea  
Diarrhea is included in the proposed labeling as well as guidance on its management.
- Rash  
Rash (including dermatitis acneiform) is in the proposed label.

#### CONCLUSION

The OSE Risk Management Team has reviewed the submitted RMP and following consultation with DDOP has determined that the serious safety issues with lapatinib are consistent with those of other cancer therapies. Both the DDOP and OSE agree that the Sponsor's proposal for routine risk management measures including labeling and routine pharmacovigilance are sufficient at this time. We refer the Sponsor to the risk management guidance documents below if they identify a safety concern that they believe warrants a RiskMAP or an enhanced Pharmacovigilance Plan.

Development of Use of Risk Minimization Action Plans:  
<http://www.fda.gov/cder/guidance/6358fnl.htm> and

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:  
<http://www.fda.gov/cder/guidance/6359fnl.htm>

Should the review division wish OSE to review a proposed RiskMAP Phase IV protocols or epidemiological post-marketing studies in the future for this product, please provide a consult request.

**OSE Risk Management Team**

Mary Dempsey, Risk Management Program Coordinator, OSE-IO

Claudia B. Karwoski, Pharm.D., Team Leader Risk Management Team, OSE-IO

**APPEARS THIS WAY  
ON ORIGINAL**

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/s/

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Mary Dempsey  
3/8/2007 10:03:06 AM  
DRUG SAFETY OFFICE REVIEWER

Ellis Unger  
3/9/2007 11:32:36 AM  
MEDICAL OFFICER

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** March 8, 2007

**TO:** Robert Justice, M.D., Director  
Division of Drug Oncology Products

**VIA:** Kim Robertson, Regulatory Project Manager  
Division of Drug Oncology Products

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support

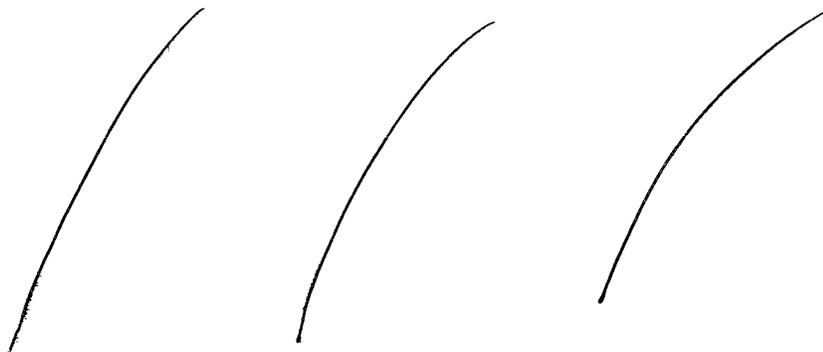
**THROUGH:** Toni Piazza-Hepp, Pharm.D., Deputy Director  
Division of Surveillance, Research, and Communication Support

**SUBJECT:** OSE/DSRCS Review of Patient Labeling for Tykerb (lapatinib)  
Tablets, NDA 22-059

**Background and Summary**

Glaxo-Smith-Kline submitted an NDA for Tykerb (lapatinib) Tablets, NDA 22-059, on September 13, 2006, for the Indication of (revised): "TYKERB, a kinase inhibitor, is indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab."

Submitted labeling included Full Prescribing Information (FPI) and a Patient Package Insert (PPI). OSE/DSRCS was consulted to review the PPI.



B

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✓ Draft Labeling

       Deliberative Process

**Robertson, Kim**

---

**From:** Robertson, Kim  
**Sent:** Friday, March 02, 2007 5:23 PM  
**To:** 'Rich.Swenson@gsk.com'; 'robert.s.watson@gsk.com'  
**Subject:** NDA 22-059 TYKERB (lapatinib)

**Importance:** High

**Attachments:** Phase 4 Commitments.doc; 02Mar07 Label Revisions (post).doc; Clean Copy of 02Mar07 Label Revisions (post).doc

Richard/Robert:

Please find the attached copies of the TYKERB label (both in Clean and Tracked Changes form), as well as the Phase 4 Commitments. Please provide the Agency with a GSK response no later than Monday, March 5, 2007.

Please call me if either of you have any questions.

Regards,  
Kim



Phase 4  
Commitments.doc (91 K)



02Mar07 Label  
Revisions (post)...



Clean Copy of  
02Mar07 Label Re...

*Kim J. Robertson*

Food and Drug Administration  
Consumer Safety Officer  
Division of Drug Oncology Products  
(301) 796-1441  
(301) 796-9845 (fax)  
kim.robertson@fda.hhs.gov

# FOOD AND DRUG ADMINISTRATION OFFICE OF DRUG EVALUATION I



## DIVISION OF DRUG ONCOLOGY PRODUCTS

HFD-150, 5600 Fishers Lane  
Rockville, Maryland 20857

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

PHONE: (301)796-2330 FAX: (301) 796-9845

TO: Richard Swenson, Ph.D., Director  
Fax: (610) 787-7062

FROM: Kim J. Robertson, CSO  
Phone: (301) 796-1441

Total number of pages, including cover sheet 2

Date: March 2, 2007

RE: NDA 22-059 TYKERB-Draft and Clean copies of label with FDA Mark-ups

COMMENTS: Richard, also please find attached to this cover page the Post Marketing Commitments that GlaxoSmithKline will need to fulfill. Please provide this information with proposed dates of fulfillment to the Agency no later than March 5, 2007 (both e-mail and officially to your NDA).

Thank you very much,  
Kim Robertson  
Consumer Safety Officer

C

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**METHODS VALIDATION MATERIALS RECEIVED**

NDA 22-059

Ms. Sherry Watson  
Director, New Submissions North America  
Global CMC Regulatory Affairs  
GlaxoSmithKline  
P. O. Box 13398  
Five Moore Drive  
Research Triangle Park, NC 27709-3398

Dear Ms. Watson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tykerb (Lapatinib Ditosylate) Tablets, 250mg and to our December 20, 2006 letter requesting sample materials and equipment for methods validation testing.

We acknowledge receipt on February 14, 2007 of the sample materials and equipment that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have any questions, you may contact me by telephone (314-539-3866), FAX (314-539-2113), or email ([duckhee.toler@fda.hhs.gov](mailto:duckhee.toler@fda.hhs.gov)).

Sincerely,

*{See appended electronic signature page}*

Duckhee Toler  
Chemist  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/

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Duckhee Toler  
2/15/2007 09:36:22 AM

## MEMORANDUM OF TELECON

DATE: December 8, 2006

APPLICATION NUMBER: NDA 22-059, Tykerb (lapatanib ditosylate) Tablets

BETWEEN:

Name: Sherry Watson, Director, Global New Submissions  
Giselle Limentani, Director of Product Development  
Martyn Voyle, Director, Synthetic Chemistry  
Nigel Richardson, Manager, Analytical Chemistry  
Girish Pande, Manager, Product Development  
Barry Carter, Investigator, Product Development

Representing: GSK

AND

Office of New Drug Quality Assessment

Chi-wan Chen, Deputy Director

Craig Bertha, Chemist, Division of Pre-Marketing Assessment I

Xiao Hong Chen, Chemist, Division of Pre-Marketing Assessment I

Terry Ocheltree, Chemist, Division of Manufacturing Science

Amy Bertha, Regulatory Health Project Manager

Representing: FDA

SUBJECT: Discuss December 6, 2006 IR letter

NDA 22-059, Tykerb (lapatanib ditosylate) Tablets, is for the treatment of patients with refractory advanced or metastatic breast cancer and was submitted on September 13, 2006. The PDUFA user fee date is March 13, 2007. This NDA is part of the CMC pilot program. An IR letter was sent on October 25, 2006 and teleconferences took place on November 6 and 16, 2006 to clarify questions in the IR letter. A second IR letter was sent on December 6, 2006 and FDA requested this teleconference to give GSK the opportunity to ask clarifying questions and get GSK's timelines for responding.

Meeting Discussion:

- FDA explained that one of the purposes of this meeting was to encourage GSK to respond to the IR letter as quickly as possible. GSK asked if FDA would consider a partial response to questions 4-7. FDA said that their first preference would be a full response to the IR letter before the action date, however questions 4-7 do not contain approvability issues. A full response to questions 1-3 is needed before the action date. FDA asked when GSK anticipated sending a response. GSK is targeting submitting

D

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- In general discussion, GSK asked if dialogue would continue if responses to all the questions could not be submitted by next week. FDA is committed to continuing the dialogue.

*{See appended electronic signature page}*

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Amy Bertha  
Regulatory Health Project Manager

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/s/

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Amy Bertha  
1/25/2007 09:59:49 AM  
PROJECT MANAGER FOR QUALITY

## Robertson, Kim

---

**From:** robert.s.watson@gsk.com  
**Sent:** Friday, December 22, 2006 4:13 PM  
**To:** Robertson, Kim  
**Cc:** Ibrahim, Amna; Ko, Chia-wen (Kiki); Ryan, Qin; Sridhara, Rajeshwari; Rich.Swenson@gsk.com; Justice, Robert; Pease, Dorothy W; Cross Jr, Frank H; Pope, Sarah  
**Subject:** Re: NDA 22-059 Tykerb Request for Information EGF 100151  
**Attachments:** Tykerb QR cover.pdf; Tykerb AI cover.pdf; Tykerb BA-BE cover Dec 22.pdf; Tykerb CRF cover.pdf; Tykerb 4 cases cover.pdf; emfinfo.txt

Kim,

We are making five submissions to the NDA today.

- Response to Dr. Ryan from 14Dec email with clarifications and additional text per Dec 20 teleconference with Reviewers
- Response to Dr. Ibrahim from 15Dec email with clarifications and additional text per Dec 20 teleconference with Reviewers
- Response to Dr. Williams providing HER2 data from eligibility criteria worksheets
- From Dec 20 TC, list of all progressors and case report forms for these subjects\*
- From Dec 20 TC, detailed information on four patients as requested by Dr. Sridhara

\*This replies in full to item 3 of your email below. Responses to Items 1 and 2 will be provided in the new year.

Cover letters are pasted into this email. The complete submissions are going to FDA today electronically via the gateway.

Please call if you have any questions. Thank you.

Happy Holidays!

Robert S. Watson  
Vice President  
US Regulatory Affairs Oncology  
robert.s.watson@gsk.com  
Office 919-483-6972  
Mobile 919-323-0223

"Robertson, Kim" <kim.robertson@fda.hhs.gov>

22-Dec-2006 12:47

To Rich.Swenson@gsk.com  
robert.s.watson@gsk.com, "Ibrahim, Amna" <amna.ibrahim@fda.hhs.gov>,  
"Ryan, Qin" <qin.ryan@fda.hhs.gov>, "Sridhara, Rajeshwari"  
cc <rajeshwari.sridhara@fda.hhs.gov>, "Ko, Chia-wen (Kiki)"  
<chiawen.ko@fda.hhs.gov>, "Justice, Robert" <robert.justice@fda.hhs.gov>  
Subject NDA 22-059 Tykerb Request for Information EGF 100151

3/12/2007

Hello Richard:

Below, please find FDA's Information Request on Study EGF100151, December 22, 2006.

1. Please provide two data sets, one for 15Nov2005 cut-off and the other for 03Apr2006 cut-off with the following information:

Subject id

Treatment group

Date of randomization

Dates of all tumor assessments by INV

Lesion location by INV

Lesion size by INV

Date of tumor assessment by IRC

Lesion location by IRC

Lesion size by IRC

Response assessment by INV

Response assessment by IRC

Date of alternative therapy

Date of censoring for INV TTP analysis

Reason for censoring as recorded by INV

Date of censoring for IRC TTP analysis

Reason for censoring as recorded by IRC

If yes for an event, then what was the event

Death date

Date of TTP event

2. Please provide pathology reports documenting the HER2-neu status for the 50 patients from the table below. The patients should have been alive at the April 3<sup>rd</sup>

3/12/2007

cut-off date. Please choose the patients in the order listed. This request supersedes the request for pathology reports on all patients on study. The request from Dr. Gene Williams for the investigator checklist on all patients is not affected by this request.

No.	Center ID or location	Patients enrolled
1.	92434 (US)	4
2.	90960 (US)	4
3.	90597 (US)	4
4.	90578 (US)	4
5.	91328 (US)	3
6.	92476 (US?)	3
7.	91325 (US)	3
8.	92745 (US)	2
9.	92729 (US)	2
10.	92728 (US)	2
11.	92709 (US)	2
12.	92364 (US)	2
13.	91482 (UK)	13
14.	92156 (France)	12
15.	91448 (Poland)	12
16.	91450 (Poland)	11
17.	90728 (Canada)	5
18.	90525 (Canada)	4

Note: Site selection is based on enrollment numbers. For patients for whom a pathology report is not available, please provide the death certificate. Alternatively, a signed statement from the investigator would be acceptable.

3. Please provide CRFs for all patients who progressed by INV or IRC assessment.

Thank you,

Kim

*Kim J. Robertson*

Food and Drug Administration

Consumer Safety Officer

Division of Drug Oncology Products

(301) 796-1441

(301) 796-9845 (fax)

[kim.robertson@fda.hhs.gov](mailto:kim.robertson@fda.hhs.gov)

3/12/2007



NDA 22-059

Page 2

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3866), FAX (314-539-2113), or email ([duckhee.toler@fda.hhs.gov](mailto:duckhee.toler@fda.hhs.gov)).

Sincerely,

*{See appended electronic signature page}*

Duckhee Toler  
Chemist  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/

Duckhee Toler

12/20/2006 04:21:05 PM

# MEMORANDUM

**To:** Kim Robertson  
DDOP

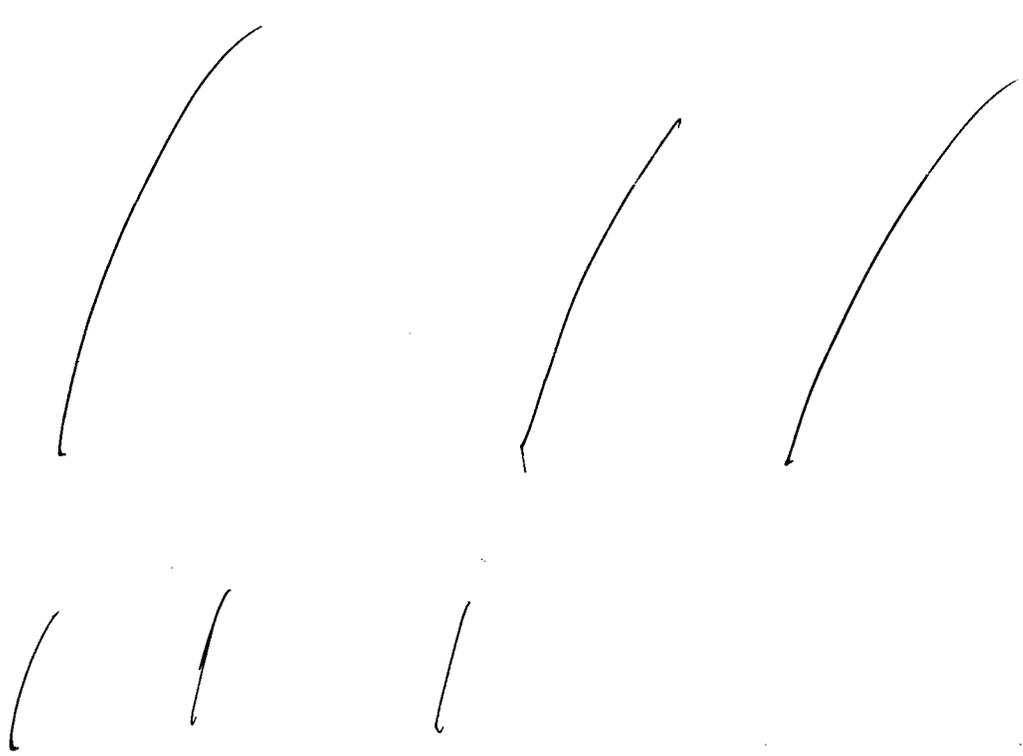
**From:** Iris Masucci, PharmD, BCPS  
for Study Endpoints and Label Development (SEALD) Team, OND

**Date:** December 15, 2006

**Re:** Comments on draft labeling for Tykerb (lapatinib) tablets  
NDA 22-059

---

We have reviewed the proposed label for Tykerb (FDA's revised version dated 12/12/06) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

The bottom of the page contains several handwritten marks. There are three large, curved, upward-sweeping lines in the upper half of this section, and three smaller, similar curved lines below them. These appear to be scribbles or initials.

E

10 Page(s) Withheld

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✓ Draft Labeling

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/s/

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Iris Masucci  
12/19/2006 09:46:08 AM  
DDMAC REVIEWER

Laurie Burke  
12/19/2006 04:53:47 PM  
INTERDISCIPLINARY

**Poochikian, Guiragos K**

---

**From:** Poochikian, Guiragos K  
**Sent:** Friday, December 08, 2006 11:20 AM  
**To:** CDER DocAdmin, DFS; Robertson, Kim; Pope, Sarah; Bertha, Amy; 'Chidambaran@cder.fda.gov'; Bertha, Craig M; Ocheltree, Terrance; Harapanhalli, Ravi S; Chen, Xiao H; Lostritto, Richard T  
**Subject:** RE: DFS Email - N 022059 N 000 FG 13-Sep-2006 - Forms

I concur with Dr. Bertha's recommendations. Labeling pertaining to the established name proposed in the correspondence dated December 4, 2006 with the exception of its size and prominence is acceptable. The size and prominence of the established name should be rectified.

Guirag

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

From: cderdocadmin@cder.fda.gov [mailto:cderdocadmin@cder.fda.gov]  
Sent: Thursday, November 30, 2006 2:11 PM  
To: Robertson, Kim; Pope, Sarah; Bertha, Amy; Chidambaran@cder.fda.gov; Bertha, Craig M; Ocheltree, Terrance; Harapanhalli, Ravi S; Chen, Xiao H; Poochikian, Guiragos K; Lostritto, Richard T  
Subject: DFS Email - N 022059 N 000 FG 13-Sep-2006 - Forms

Document room update the following:

Decision Date Decision Code

N 022059 N 000 FG 13-Sep-2006 30-Nov-2006 :

---

Document Type: Forms  
Form Group: CONSULT  
Form Name: General Consult Request  
Submission Description: Labeling and Nomenclature Committee Consult sn:000

---

Author(s)/Discipline(s)

1. Kim Robertson, CSO

---

Signer(s)

1. Kim Robertson  
Labeling and Nomenclature Committee Consult  
30-Nov-2006

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Supervisory Signer(s)

1. Kim Robertson  
Labeling and Nomenclature Committee Consult  
30-Nov-2006

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/s/

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Guiragos Poochikian  
12/19/2006 10:06:47 AM  
CHEMIST .

**Robertson, Kim**

---

**From:** Rich.Swenson@gsk.com  
**Sent:** Friday, December 08, 2006 11:07 AM  
**To:** Robertson, Kim  
**Subject:** Re: NDA 22-059 Tykerb  
**Attachments:** emfinfo.txt

Dear Kim:

Please refer to the FDA Email of 4 December 2006 regarding a question from the "clinpharm group" with regard to HER2 testing in NDA 22-059.

**FDA Question:**

*"The clinpharm group has not been able to find information in the label or the clinical studies that identify the specific names of the test used for HER2 overexpression by IHC or FISH. For example, was the HER2 FISH pharmDx™ or the Vysis HER2 DNA probe kit used?"*

*Can GSK pre-specify where to look in the electronic documents to find this information?*

*Alternatively, can GSK electronically provide the name of the tests for HER2 (IHC and FISH) used in the clinical studies?"*

**GSK Response:**

In the Clinical Study Report for Protocol 100151 (NDA Module 5.3.5.1; Section 5.3.1 "Inclusion/Exclusion Criteria"), we state the following:

*"Documentation of ErbB2 overexpression (immunohistochemistry (IHC) 3+ or, IHC 2+ with fluorescence in situ hybridization (FISH) confirmation) was required based on local laboratory or initial diagnostic results. Where testing was not feasible, central laboratory testing was utilized."*

Patients enrolled in EGF100151 had failed prior therapies including trastuzumab. A site may have required central testing if the original HER2 test result was not available or the result was not reported with the scoring in the IHC scale. If a site required central testing, the site was instructed to follow instructions for sample preparation and shipping instructions provided in the central laboratory manual. This laboratory manual was the same for all countries.

In countries in which EGF100151 was conducted, approved commercial kits for testing of Her2 (ErbB2) overexpression by IHC are \_\_\_\_\_, for Her2(ErbB2) amplification there are the \_\_\_\_\_

If you have any questions, please call me at (610) 787-3724; I can be reached by fax at (610) 787-7062.

3/12/2007

Regards,

rich

Richard Swenson, Ph.D.  
Senior Director, US Regulatory Affairs

3/12/2007

**Robertson, Kim**

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**From:** Ko, Chia-wen (Kiki)  
**Int:** Thursday, December 07, 2006 2:52 PM  
**To:** Robertson, Kim  
**Subject:** NDA 22059 - Reference needed

Hi Kim,

Could you kindly ask GSK to provide us a pdf copy of the following article they cited in their EGF100151 study report?

Berry et al, Statistics in Medicine, 10: 749-755 (1991)

Thanks,

Chia-Wen Ko (Kiki)  
Math Stat  
DBV/OB/CDER/FDA  
W022, RM1221  
10903 New Hampshire Ave, Silver Spring, MD 20993  
301-796-2058



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-059

**INFORMATION REQUEST LETTER**

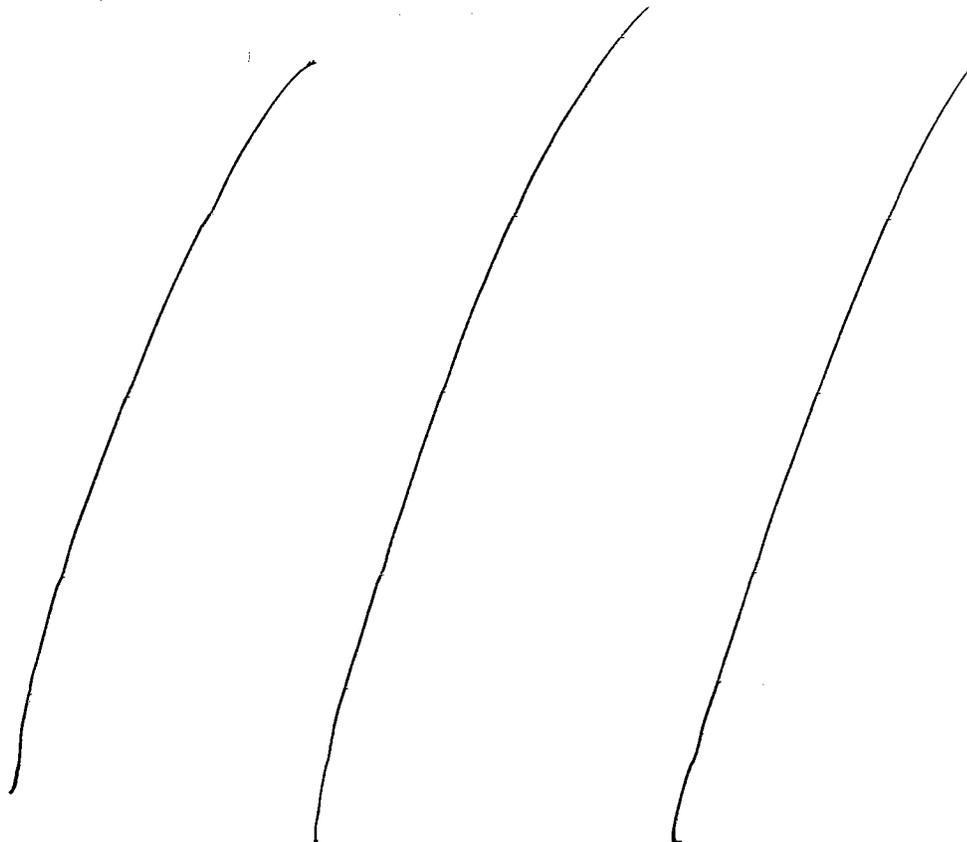
GlaxoSmithKline  
Attention: Sherry Watson, Director  
PO Box 13398  
Five Moore Drive  
Research Triangle Park, NC 27709

Dear Ms. Watson:

Please refer to your September 13, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tykerb (lapatinib ditosylate) tablets. We also refer to CMC amendments dated November 10, 2006, November 17, 2006, and December 1, 2006.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submissions and have the following comments and information requests. In order to expedite our review, we request a prompt response to comments 1-3. As such, it is suggested that you provide these responses in a separate amendment from that which addresses the Quality by Design questions in comments 4-7.

Three large, curved, handwritten lines, likely indicating redactions or a signature.



If you have any questions, call Amy Bertha, Regulatory Health Project Manager, at 301-796-1647.

Sincerely,

*{See appended electronic signature page}*

Chi-wan Chen, Ph.D.  
Deputy Director  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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

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Craig Bertha  
12/6/2006 11:06:50 AM  
for Chi-Wan Chen

# REQUEST FOR CONSULTATION

TO (Office/Division): Guiragos Poochikian, Ph.D., 6-1900

FROM (Name, Office/Division, and Phone Number of Requestor): Kim Robertson, CSO, 6-1441

DATE  
November 30, 2006

IND NO.

NDA NO.  
22-059

TYPE OF DOCUMENT  
New NDA-Clinical &  
Non-Clinical

DATE OF DOCUMENT  
September 13, 2006

NAME OF DRUG  
Tykerb (lapatinib) ditosylate  
tablets

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
As soon as possible; Div.  
Action Date is 12/15/06

NAME OF FIRM:

## REASON FOR REQUEST

### I. GENERAL

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

### II. BIOMETRICS

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

### III. BIOPHARMACEUTICS

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

### IV. DRUG SAFETY

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

### V. SCIENTIFIC INVESTIGATIONS

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

COMMENTS / SPECIAL INSTRUCTIONS: Dr. Poochikian, the Division of Drug Oncology Products is requesting a review of this new NME NDA based on recommendation from DMETS with regard to this drug's proper designation of the established name. The MO is Qin Ryan, M.D., Ph.D.; Proj. Mgr. is Kim Robertson

SIGNATURE OF REQUESTOR  
Kim Robertson

METHOD OF DELIVERY (Check one)

- DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

**Bertha, Amy**

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**From:** Bertha, Amy  
**Sent:** Wednesday, November 29, 2006 11:06 AM  
**To:** 'sherry.l.watson@gsk.com'  
**Subject:** Lapatinib, NDA 22-059, follow up to 16.Nov2006 FDA & GSK teleconference

Sherry-

The following are comments we are providing as a follow-up to the November 16, 2006 teleconference (Lapatinib, NDA 22-059):

1) At the November 16, 2006 teleconference we had two options that we recommended concerning the drug name and strength for the label as a follow up to comment 7 of the October 25, 2006 IR letter. As an action item we said we would provide these two options in writing:

(1) Change the established name of the drug product to lapatinib tablets while retaining the strength as 250 mg and including a footnote stating "each tablet contains 398 mg lapatinib ditosylate equivalent to 250 mg lapatinib," or

\*\*As a clarification, please note that the statement we said at the teleconference

We acknowledge receipt of an email from Richard Swenson from GSK on November 17, 2006 (and subsequent NDA amendment submission) containing a new proposed container label. We have reviewed this proposal, and it is unacceptable. We strongly recommend you adopt one of the above two established name/strength options.

2) Thank you for your two responses to our information request for \_\_\_\_\_ analysis [reference is made to your November 10, 2006 response to Question 1c of the October 25, 2006 IR letter and your response sent to us via email on November 16, 2006 (and subsequent NDA amendment submission) to our request from the November 16, 2006 teleconference]

3) In the November 16, 2006 teleconference, we discussed the regulatory agreement.

agreement issue will be addressed in the action letter.

The regulatory

Additionally, indicate where and how you will capture that the drug substance will be tested for \_\_\_\_\_ impurity within 90 days of formulation, e.g. drug substance specification sheet, drug product specification sheet, batch record.

A copy of this correspondence has been placed in the NDA 22-059 administrative file.

We request a prompt response to these question in order that we can continue the NDA review. As with the responses you sent us in regards to the October 25, 2006 IR letter, we would appreciate receiving an electronic version of your responses (in addition to the official response you will send to the NDA).

Please note we will be sending Quality by Design related questions separately.

Thank you, amy

*Amy Bertha*  
Regulatory Health Project Manager  
Office of New Drug Quality Assessment  
OPS/ CDER/ FDA  
tel: 301.796.1647  
amy.bertha@fda.hhs.gov

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

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Amy Bertha  
11/29/2006 02:20:36 PM  
PROJECT MANAGER FOR QUALITY