

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206995Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 206995

SUPPL #

HFD #

Trade Name Iressa

Generic Name gefitinib

Applicant Name AstraZeneca UK Ltd.

Approval Date, If Known pending – PDUFA date is July 17, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. 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:

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

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# 21399

Iressa (gefinitib)

Received accelerated approval on May 5, 2003. Voluntarily withdrawn in September 2011. Date of Federal Register notice was April 25, 2012.

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

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

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

Study D79AC00014 (IFUM) – a multicenter, single –arm study to characterize the efficacy of gefitinib 250 mg (once daily) as first-line treatment in Caucasian patients with EGFR mutation-positive, locally advanced or metastatic NSCLC.

This study was not conducted under an IND.

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

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

Investigation #1 !
IND # YES ! NO
! Explain:

Investigation #2 !
IND # YES ! NO
! Explain:

Name of person completing form: Sharon Sickafuse
Title: Senior Regulatory Health Project Manager
Date: 6-12-2015

Name of Office/Division Director signing form: Patricia Keegan, M.D.
Title: Director, Division of Oncology Products 2

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

SHARON K SICKAFUSE
06/30/2015

PATRICIA KEEGAN
06/30/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 206995 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Iressa Established/Proper Name: gefitinib Dosage Form: tablets		Applicant: AstraZeneca UK Limited Agent for Applicant (if applicable):
RPM: Sharon Sickafuse		Division: DOP2
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) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>7-17-2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input checked="" type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other ASCO burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 7-13-2015
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included 7-10-2015
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 1-26-2015
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 9-25-2014
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included 4-17-2015
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	12-15-2014 12-4-2014
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: 11-13-2014 DMEPA: 4-8-2015 DMPP/PLT (DRISK): 5-27-2015 OPDP: 6-2-2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	11-13-2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included 6-30-2015
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>has Orphan Drug designation for NSCLC indication</u> 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	Revised PI & PPI email 7-10-2015 Revised PI & PPI email 7-7-2015 Revised PI & PPI 6-25-2015 Clinical IR email 6-23-2015 Revised PPI email 6-12-2015 Revised PI email 6-11-2015 Biopharmaceutics IR email 5-20-15 Revised PI email 5-12-2015 Clin pharm IR email 5-7-2015 Clinical IR email 4-28-2015 Container label LTR 4-9-2015 Clinical IR email 2-17-2015 Clinical & stat IR email 12-17-2014 OSI IR email 12-10-2014 Clin Pharm IR email 12-5-2014 DI LTR 11-28-2014 OSI IR email 11-19-2014 OSI IR email 11-18-2014 Clinical IR email 11-14-2014 QT data IR email 11-13-2014 QT data IR email 11-10-2014 Nonclinical IR email 11-4-2014 OSI IR email 10-9-2014 ACK LTR 9-29-2014
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	Wrap-up MS 6-8-2015 MidCycle MS 2-17-2015 Planning MS 10-29-2014 Review Schedule Designation 10-9-2014
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	3-11-2014
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	

❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7-13-2015
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	6-4-2015
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	Signed concurrence on 5-29-2015 review
• Clinical review(s) (<i>indicate date for each review</i>)	5-29-2015
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Pages 34 & 35 of 5-29-2015 review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	6-15-2015 (letter to CRO) 4-24-2015 (review)
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review signed concurrence on 5-22-2015 review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	Signed concurrence on 5-22-2015 review
Statistical Review(s) (<i>indicate date for each review</i>)	5-22-2015

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review signed concurrence on 5-22-2015 review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	Signed concurrence on 5-22-2015 review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	5-22-2015, 4-15-2015 (QT-IRT review)
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	Signed concurrence on 5-21-2015 review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	5-21-2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	Signed concurrence on 5-21-2015 & 5-13-2015 reviews
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	5-21-2015 (biopharmaceutics); 5-13-2015 (product)
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	11-6-2014
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Page 23 of 5-13-2015 review
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵</i>)	Date completed: 5-15-2015 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/

NORMA S GRIFFIN
07/15/2015

Griffin, Norma

From: Griffin, Norma
Sent: Friday, July 10, 2015 3:27 PM
To: 'Wible, Renee'
Cc: Sickafuse, Sharon; Caster, Donna M
Subject: RE: AstraZeneca NDA 206995 "IRESSA" - FDA Proposed Edits - Final DRAFT Labeling
Attachments: 7.10.2015 FDA Proposed Edits to Sponsor CLEAN.doc; 7.10.2015 FDA Proposed Edits to Sponsor tracked changes.pdf

Importance: High

Renee,

The Team has reviewed your labeling and found it acceptable with the addition of a few minor edits. We made the edits on your non-annotated CLEAN version. Please see our attached Tracked Changes PDF version and our CLEAN WORD version.

Can you please push through the Gateway today the FINAL Draft Labeling with these agreed changes? This is so that we can keep our schedule for taking action next week.

Kindly respond to confirm receipt of this email and the attached labeling.

Norma S. Griffin

Senior Regulatory Health Project Manager

CDER / OHOP / DOP2

Telephone 301.796.4255

From: Wible, Renee [<mailto:Renee.Wible2@astrazeneca.com>]
Sent: Friday, July 10, 2015 12:49 PM
To: Griffin, Norma
Cc: Sickafuse, Sharon; Caster, Donna M
Subject: RE: AstraZeneca NDA 206995 "IRESSA" - FDA Proposed Edits - Final Agreed

Hi Norma,

This is to let you know that the labeling, subject of the attached email, has been officially submitted through the Gateway to amend the NDA (206995, Sequence 0025).

Since my email yesterday, a last minute quality check revealed the need to amend Section 6.1, Study 2, Study 3 and Study 4 with regard to the numbers of patients who received drug. This change is included in the non annotated (Clean) label and annotated label provided here as Word documents and in the submission provided today. AstraZeneca regret needing to make this change late in the process but want to ensure that the accurate information is provided in the label to FDA.

Please confirm receipt of this email and attachments.

Best,
Renée S. Wible
AstraZeneca, Oncology
Sr. Global Regulatory Director
Mobile +1 302 898 3528

From: Wible, Renee
Sent: Thursday, July 09, 2015 1:08 PM
To: 'Griffin, Norma'
Cc: 'Sickafuse, Sharon'; Caster, Donna M
Subject: RE: AstraZeneca NDA 206995 "IRESSA" - FDA Proposed Edits - Final Agreed

Good Morning Norma,

AstraZeneca agree with the final labeling however, an error was found in Table 1 footnotes; the adverse reaction terms listed are from the pooled Studies 2, 3 and 4 (N= 2462). AZ has updated the footnotes to reflect the adverse drug reactions reported in Study 1 as is appropriate.

In addition, there is an error in 5.6 Bullous and Exfoliative Skin Disorders, the second sentence, "Erythema multiforme and dermatitis bullous (0.08%) have been reported in two patients (0.08%) across NSCLC trials (Study (b) (4) Study 2 and Study 3)." This was correct in the June 11, 2015 version but was incorrectly transcribed as (b) (4) % in later versions. This has been corrected.

Attached are the clean (non annotated WORD document) and the annotated WORD document.

AZ will follow up with a formal submission to amend the NDA.

Please do not hesitate to contact me if you have questions.

Please confirm receipt of this message and the attached labeling.

Best,
Renée S. Wible
AstraZeneca, Oncology
Sr. Global Regulatory Director
Mobile +1 302 898 3528

From: Griffin, Norma [<mailto:Norma.Griffin@fda.hhs.gov>]
Sent: Tuesday, July 07, 2015 3:34 PM
To: Wible, Renee
Cc: Sickafuse, Sharon; Caster, Donna M
Subject: AstraZeneca NDA 206995 "IRESSA" - FDA Proposed Edits from today's TCON
Importance: High

Good Afternoon Renee,

As discussed and agreed to in today's teleconference, please see the attached labeling with FDA's proposed edits and comments. I have provided both a CLEAN (edits accepted) WORD document and an annotated PDF version.

Please provide your response/agreement and final labeling (clean WORD document) to me via email by Thursday, July 9, 2015, or sooner if possible and follow with an official submission to NDA 206995.

Kindly respond to confirm receipt of this email and the attached labeling.

Norma S. Griffin
Senior Regulatory Health Project Manager
CDER / OHOP / DOP2
Telephone 301.796.4255

Confidentiality Notice: This message is private and may contain confidential and proprietary information. If you have received this message in error, please notify us and remove it from your system and note that you must not copy, distribute or take any action in reliance on it. Any unauthorized use or disclosure of the contents of this message is not permitted and may be unlawful.

34 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

NORMA S GRIFFIN
07/10/2015

Griffin, Norma

From: Griffin, Norma
Sent: Tuesday, July 07, 2015 3:34 PM
To: 'Wible, Renee'
Cc: Sickafuse, Sharon; Caster, Donna M
Subject: AstraZeneca NDA 206995 "IRESSA" - FDA Proposed Edits from today's TCON
Attachments: FDA 7 7 2015 Proposed Edits annotated-draft-labeling to Sponsor.pdf; FDA 7 7 2015 Proposed Edits CLEAN labeling to Sponsor.doc

Importance: High

Good Afternoon Renee,

As discussed and agreed to in today's teleconference, please see the attached labeling with FDA's proposed edits and comments. I have provided both a CLEAN (edits accepted) WORD document and an annotated PDF version.

Please provide your response/agreement and final labeling (clean WORD document) to me via email by Thursday, July 9, 2015, or sooner if possible and follow with an official submission to NDA 206995.

Kindly respond to confirm receipt of this email and the attached labeling.

Norma S. Griffin
Senior Regulatory Health Project Manager
CDER / OHOP / DOP2
Telephone 301.796.4255

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/s/

NORMA S GRIFFIN
07/07/2015



NDA 206995

INFORMATION REQUEST

AstraZeneca UK Limited
Attention: Renee Wible
Senior Director, Global Regulatory Affairs
AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Ms. Wible:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IRESSA (gefitinib) 250 mg tablets.

FDA's proposed revisions to the package insert and patient package insert are attached.

If you have any questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:

Revised Package Insert
Revised Patient Package Insert

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/s/

SHARON K SICKAFUSE
06/25/2015

From: Sickafuse, Sharon
Sent: Tuesday, June 23, 2015 3:04 PM
To: renee.wible2@astrazeneca.com; Caster, Donna M
(donna.caster@astrazeneca.com)
Subject: Iressa clinical IR

Importance: High

Hi Renee & Donna,

My team has the following IR:

Please specify all sites of disease (including lung, pleural, peritoneal, nodal, and extra-thoracic) for the 8 patients in IFUM and the 16 patients in IPASS identified as locally advanced.

Please provide this data by COB Wednesday, June 23 via email with a follow-up amendment to the NDA

Thanks

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/s/

SHARON K SICKAFUSE
06/23/2015



NDA 206995

INFORMATION REQUEST

AstraZeneca UK Limited
Attention: Renee Wible
Senior Director, Global Regulatory Affairs
AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Ms. Wible:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IRESSA (gefitinib) 250 mg tablets.

FDA's proposed revisions to the patient package insert are attached.

If you have any questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Revised Patient Package Insert

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SHARON K SICKAFUSE
06/12/2015



NDA 206995

INFORMATION REQUEST

AstraZeneca UK Limited
Attention: Renee Wible
Senior Director, Global Regulatory Affairs
AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Ms. Wible:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IRESSA (gefitinib) 250 mg tablets.

FDA's proposed revisions to the package insert are attached.

If you have any questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Revised Package Insert

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/s/

SHARON K SICKAFUSE
06/11/2015

NDA REVIEW WRAP-UP MEETING SUMMARY
June 8, 2015

NDA 206995
Iressa (gefitinib)

Proposed Indication: IRESSA is indicated for the first-line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R or L861Q) or exon 18 (G719X) substitution mutations as detected by an FDA-approved test.

Limitation of Use: Safety and efficacy of IRESSA have not been established in patients whose tumors have (b) (4) exon (b) (4) mutations in the EGFR.

Action Due Date: July 17, 2015

Proposed Early Action Date: July 1, 2015

Dates That Outstanding Signed Reviews Are Due:

Division Director	6-26-2015
Office Director	7-17-2015 (7-1-2015)

Discuss Remaining Outstanding Pre-Action Items:

1. Labeling:

- a. Revised container labeling received April 17th. Revised labeling has addressed all FDA comments and is acceptable.
- b. Revised PI received on May 27th. Internal meeting scheduled for June 8th. Labeling is still being negotiated. Plan to send revised PI & Med Guide to AZ this week.
- c. Patient labeling review of Med Guide received on May 27th. Based on the outcome from the internal labeling meeting, patient labeling may have additional revisions.

2. PMCs and PMRs: none requested

3. Employee list (yes/no) for Action Package: Emailed on June 2nd

4. Press Release/ASCO Burst: Press office has been notified.

6. **Action Package Preparation:** Will give to CPMS this week.
7. **Approval letter:** In draft. Need to circulate to team once indication wording has been agreed upon.
8. **Exclusivity summary:** Has been prepared. Need to email to Dr. Keegan.

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/s/

SHARON K SICKAFUSE
06/08/2015

From: Biable, Missiratch (Mimi)
To: [Wible, Renee \(Renee.Wible2@astrazeneca.com\)](mailto:Wible.Renee(Renee.Wible2@astrazeneca.com)); [Caster, Donna M \(donna.caster@astrazeneca.com\)](mailto:Caster.Donna.M(donna.caster@astrazeneca.com))
Cc: [Sickafuse, Sharon](#)
Subject: NDA 206995: Information Request -- Response Required
Date: Wednesday, May 20, 2015 11:26:00 AM
Importance: High

Dear Renee and Donna,

I am sending you the following on behalf of Sharon Sickafuse who is currently out of the office.

The Biopharmaceutics team has the following information request that we wish you to address before COB **Thursday, May 21, 2015**.

Your proposed dissolution acceptance criterion, as stated in the specifications table, is not acceptable. Update the dissolution acceptance criterion as follows:

$Q = \frac{(b)}{(4)}\%$ at 45 min

Please provide the updated specifications table via email to me and Sharon Sickafuse and follow that with a formal submission to your NDA.

Regards,

Missiratch (Mimi) Biable, M.S., R.A.C (US)
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Email: Missiratch.biable@fda.hhs.gov
Phone: 301-796-0154

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/s/

MISSIRATCH BIABLE
05/20/2015



NDA 206995

LABELING PMR/PMC DISCUSSION COMMENTS

AstraZeneca UK Limited
Attention: Renee Wible
Senior Director, Global Regulatory Affairs
AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Ms. Wible:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IRESSA (gefitinib) 250 mg tablets.

We also refer to our November 28, 2014, letter in which we notified you of our target date of May 29, 2015, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On January 26, 2015, we received your January 26, 2015, proposed labeling submission to this application, and have proposed revisions that are included as an enclosure. We request that you resubmit labeling that addresses these issues by May 27, 2015. The resubmitted labeling will be used for further labeling discussions.

Your proposed prescribing information (PI) must conform to the content and format regulations found at [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). Prior to resubmitting your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

If you have any questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Revised Package Insert

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/s/

SHARON K SICKAFUSE
05/12/2015

From: Sickafuse, Sharon
Sent: Thursday, May 07, 2015 2:32 PM
To: renee.wible2@astrazeneca.com; Caster, Donna M
(donna.caster@astrazeneca.com)
Subject: NDA 206995 clin pharm IR

Hi Renee & Donna,

My clin pharm team has the following IR:

Based on study report D7913C00019, CYP2D6 poor metabolizers had 2.1-fold higher exposure to gefitinib compared to CYP2D6 extensive metabolizers. However, no CYP2D6 ultra-rapid metabolizers were included in the study. Please provide any pharmacokinetic data available comparing CYP2D6 ultra-rapid metabolizers to CYP2D6 extensive metabolizers.

Please provide this information by Thursday, May 14th. Thank you

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/s/

SHARON K SICKAFUSE
05/07/2015

From: Sickafuse, Sharon
Sent: Tuesday, April 28, 2015 4:13 PM
To: renee.wible2@astrazeneca.com; Caster, Donna M
(donna.caster@astrazeneca.com)
Subject: NDA 206995 clinical IR

Hi Renee and Donna,

My clinical team has the following IR:

To potentially better inform Section 1 'Indications and Usage' and 'Limitation of Use' and Section 2.1 'Patient Selection' sections of product labeling, please query the IRESSA clinical and non-clinical evidence base (including published literature) to develop case definitions for EGFR "activating sensitizing" mutations (e.g. exon 19 deletion, L858R, and other uncommon mutations), EGFR "activating resistance" mutations (e.g. T790M, exon 20 insertion, and other uncommon mutations), as well as any "indeterminate" mutations of unknown significance. These case definition should be based on available clinical and pre-clinical evidence. In addition to the case definitions, provide the evidence supporting these definitions.

Please provide this information by COB May 19.

Thank you

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/s/

SHARON K SICKAFUSE
04/28/2015



NDA 206995

INFORMATION REQUEST

AstraZeneca UK Limited
Attention: Renee Wible
Senior Director, Global Regulatory Affairs
AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Ms. Wible:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IRESSA (gefitinib) 250 mg tablets.

We have the following comments regarding the container labeling:

1. Revise the container label to include the unit of measurement immediately following numerical temperature values. We note that the unit of measurement (e.g. °C) is missing immediately following numerical temperature values on the side panel. For example, revise “Store at controlled room temperature, 20 - 25°C (68 - 77°F)” to read “Store at controlled room temperature, 20°C - 25°C (68°F - 77°F).”
2. Revise the established name to ensure that it is at least half as large as the proprietary name and prominence commensurate with the proprietary name in accordance with 21 CFR 201.10(g)(2).
3. Remove the statement [REDACTED] (b) (4) (b) (4)
4. We note the presence of numbers “00000-00” directly above the placeholder intended for lot and expiration numbers. Consider decreasing the prominence of this number and relocating this number “00000-00” away from the lot number & expiration date because as currently presented ,it can create confusion with the lot number or expiration date.

Please submit revised carton labels.

If you have any questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

SHARON K SICKAFUSE
04/09/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs Evaluation and Research

Memorandum

Date: February 17, 2015

From: Sharon Sickafuse, RPM

NDA: 206995

Product: (b) (4) (gefitinib)

Applicant: AstraZeneca UK Limited

Subject: Mid-Cycle Review Meeting

Major Findings/Issues:

1. The team determined that there is a positive risk-benefit assessment for Iressa in the first-line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutation(s) as detected by an FDA-approved test (Qiagen *therascreen* EGFR RGQ PCR kit). The team recommended approval of the NDA.
2. The pharmacometrics team presented their findings that patients with a moderate and severe hepatic impairment due to cirrhosis had a 3.6- and 2.7-fold increase in exposure to Iressa, respectively. In addition, patients with CYP2D6 poor metabolism have a 2.1-fold increase in exposure compared to patients that don't. The pharmacometrics team is considering recommending that the dosing for these patients be decreased and that the labeling reflect this. As Iressa has been approved in Europe since 2009, Dr. Pazdur recommended that the team have a teleconference with EMA to discuss their concerns.
3. Jennifer Shen of CDRH stated that CDRH issued a letter to Qiagen on December 23, 2014, regarding Qiagen's premarket approval application (PMA) supplement which requested approval for adding an IRESSA™ (gefitinib) indication in the intended use of the QIAGEN *therascreen*® EGFR RGQ PCR Kit. The letter

stated the deficiencies in the supplemental PMA and requested that Qiagen respond by June 21, 2015.

Status of OSI Inspections:

IRC/CRO site (b) (4) inspection scheduled for (b) (4)

Status of Facility Inspections:

The drug substance is manufactured at the following contract sites:

(b) (4)

The (b) (4) facility has not been inspected by FDA since 2008. This site was inspected by FDA in January and we are waiting on the inspection report and evaluation of the site.

The drug product is manufactured at the AstraZeneca UK Ltd. site in the UK.

Status of PMRs/PMCs:

At this point, the team does not plan to request any PMR(s)/PMC(s).

REMS:

At this point, the team does not anticipate that a REMS will be needed.

Press Release/ASCO Burst:

OHOP will issue a press release and an ASCO Burst.

Labeling Meetings Scheduled:

Clinical & Stats (sections 1 & 14)	March 30 th
CMC, DMEPA & Clinical	April 14 th
Clinical & Nonclinical	April 27 th
Clin Pharm & Clinical	April 28 th
Clinical (sections 4, 5, 6 & 17)	May 4 th

Labeling needs to be sent to AstraZeneca by May 29, 2015.

Wrap-Up meeting TBD

Review Due Dates:

Primary Review	5-22-2015
Secondary Review	5-29-2015
CDTL Review	6-5-2015
Division Director Review	6-26-2015
Office Director Review	7-17-2015

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/s/

SHARON K SICKAFUSE
02/23/2015

From: Sickafuse, Sharon
Sent: Tuesday, February 17, 2015 5:43 PM
To: renee.wible2@astrazeneca.com; Caster, Donna M
(donna.caster@astrazeneca.com)
Subject: NDA 206995 - clinical IR

Hi,

My clinical reviewer has the following IR:

Regarding retrospective evaluation of EGFR mutation status in the IPASS study, AZ states that although 56% of patients provided samples only 36% were evaluable. Please further elaborate on the specific quality issues with the 20% of samples which were non-evaluable.

Thank you

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/s/

SHARON K SICKAFUSE
02/17/2015

From: Sickafuse, Sharon
Sent: Wednesday, December 17, 2014 3:29 PM
To: renee.wible2@astrazeneca.com; Caster, Donna M
(donna.caster@astrazeneca.com)
Subject: NDA 206995 - clinical & stat IR

Hi Renee & Donna,

My clinical & stat reviewers have the following IR:

Please re-create the IFUM derived analysis PDF files such that the variables and possible values are clearly defined. For example, in the one patient per row efficacy.xpt data set, the variable OBRESPC's or MUT20-3A possible values are not defined or coded in the define-analysis.PDF. Also, some of the units are missing, for example, in duration of response variable. In the RSRS.XPT data set in the analysis data set, by using the define file it is unclear, for example, what RS stands for under the variable DOMAIN, NTRGRESP in PARAMCD, what are the codes for the values in GROUP02, and what are the units for the tumor measurements for SUMDIAM.

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/s/

SHARON K SICKAFUSE
12/17/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206995

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

AstraZeneca UK Limited
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

ATTENTION: Renee S. Wible,
Senior Director, Global Regulatory Affairs

Dear Ms. Wible:

Please refer to your New Drug Application (NDA) dated September 17, 2014, received September 17, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gefitinib Tablets, 250mg.

We also refer to your October 3, 2014, correspondence, received October 3, 2014, requesting review of your proposed proprietary name, Iressa.

We have completed our review of the proposed proprietary name, Iressa and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your October 3, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application, contact Sharon Sickafuse, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1462.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
12/15/2014

From: Sickafuse, Sharon
Sent: Wednesday, December 10, 2014 1:04 PM
To: Caster, Donna M (donna.caster@astrazeneca.com)
Cc: renee.wible2@astrazeneca.com
Subject: NDA 206995 - OSI IR

Importance: High

Hi Donna,

Regarding your December 9, 2014, response to item 5 of the November 28, 2014, DI letter, the datasets provided for OSI Part III are only useful for uploading into the Site Selection Tool, and in an xpt formal, which the OSI reviewer cannot use to conduct the planned inspection of the CRO.

Please provide data listings as described below, in a PDF format, organized by Site, then Subject detailed listings. Specifically, under D791AC00014 BIMO Site-Level Data Listings, the OSI reviewer needs the following listings as determined by the CRO.

- “Subject listing h1: Primary efficacy endpoint” (determined by the CRO)
- “Subject listing h3: Primary and Secondary efficacy endpoint raw data, Target lesion details (determined by the CRO)
- “Subject listing h6: Primary and Secondary efficacy endpoint raw data, Investigator overall visit response (for the CRO)

Thank you

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/s/

SHARON K SICKAFUSE
12/10/2014

From: Sickafuse, Sharon
Sent: Friday, December 05, 2014 4:00 PM
To: renee.wible2@astrazeneca.com; Caster, Donna M
(donna.caster@astrazeneca.com)
Subject: NDA 206995 - clin pharm IR

Hi Renee & Donna,

My clin pharm team has the following IR regarding the study report, "Population Pharmacokinetic Analysis With Non Small Cell Lung Cancer In Nested Case-Control Study For Gefitinib (Study Code: V-15-33)" in module 5.5.3.5. Please conduct the following analyses:

1. Summarize the ILD (interstitial lung disease) rates by exposure (i.e., AUC, Cmax, Cmin) quartiles. Justification should be provided for the exposure metric used for the final analysis.
2. Conduct exposure-response analysis by using multivariate logistic model to assess the association of exposure and other risk factors with ILD.
3. Submit a brief report, datasets, and modeling scripts based on the requirements specified in the link (<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>).

Please submit your response by December 31.

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/s/

SHARON K SICKAFUSE
12/05/2014



NDA 206995

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

AstraZeneca UK Limited
Attention: Renee Wible
Senior Director, Global Regulatory Affairs
AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Ms. Wible:

Please refer to your New Drug Application (NDA) dated September 17, 2014, received September 17, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for IRESSA (gefitinib) 250 mg tablets.

We also refer to your amendments dated September 25, October 3, and November 3 and 7, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is July 17, 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by May 29, 2015.

During our filing review of your application, we identified the following potential review issues. Please provide a single submission containing the requested information or your timeline for providing the requested information for each item within one week of receipt of this letter.

Biopharmaceutics

The proposed dissolution method (with 5% v/v Tween 80 in water as the medium) does not exhibit discriminating power when the clinical and commercial batches, that are not bioequivalent, are compared. Based on the presented data (Table 12, 3.2.P.2.2 Drug Product – Attachment 1), the calculated f_2 score is 50.2. Provide a dissolution method that is more suitable and discriminates the two formulations that have been demonstrated to be bioinequivalent. The following general guidelines for the content of a dissolution method development report should be considered:

1. **Dissolution Test:** Include the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution development report should include the following information:
 - a. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, *in vitro* dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend the use of at least twelve samples per testing variable and sampling time points of 10, 15, 20, 30, 45, 60, 90 and 120 min.
 - b. Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim).
 - c. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10 -20% change to the specification-ranges of these variables).
2. **Dissolution Acceptance Criterion:** For the selection of the dissolution acceptance criterion(a) of your product, the following points should be considered:
 - a. The dissolution profile data (15, 20, 30, 45, 60, 90, 120 min; $n = 12$) from the pivotal clinical batches and primary (registration) batches (throughout the stability program) should be used for the setting of the dissolution acceptance criterion(a) of your product (i.e., specification sampling time point and specification value).

- b. The *in vitro* dissolution profile should encompass the timeframe over which at least 85% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
- c. The selection of the specification time point should be where $Q = \frac{(b)}{(4)}\%$ dissolution occurs. However, if you have a slowly dissolving product, specifications at two time points may be adequate for your product. The first time point should be selected during the initial dissolution phase (i.e., 15-30 minutes about 40-50% dissolution) and the second time point should be where $Q = \frac{(b)}{(4)}\%$ dissolution occurs.

Clinical

3. In Study IFUM, 17 cases were “non-measurable” according to the independent radiology review (IRR) assessments. Please describe, in detail, the sites of disease in these patients and any information from the IRR which would help explain the reason that these patients were “non-measurable.”
4. Please provide the address for (b) (4) the central review contract research organization (CRO) site that you used (i.e., Germany or the UK) and the location of the central review records for Study IFUM.
5. The NDA provides efficacy endpoint data listings for each clinical site. It appears that these listings report the tumor response as determined by the clinical investigators at each site. Please submit the efficacy data listings as determined by the CRO, so that we can verify against source at the CRO site.
6. Please provide the IRR Charter from (b) (4) so that we can confirm that the CRO performance was in accordance with not only the protocol but also the detailed Charter of exactly what and how they were to perform their IRR assessments.
7. Please submit the finalized European Union Risk Management Plan.

Biostatistics

8. Provide the SAS programs as well as format library files used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs. Provide an all-in-one SAS format library.
9. Provide the SAS programs for derived datasets and the analyses associated with the results presented in the proposed package insert.
10. Provide adequate documentation for all SAS programs.

Clinical Pharmacology

11. Please fill out the attached Highlights of Clinical Pharmacology Table and submit as an amendment to the NDA.
12. We are unable to locate the data for the QT study report. Please submit or provide the location of the following information:
 - a. Annotated CRF.
 - b. A data definition file which describes the contents of the electronic data sets.
 - c. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses.
 - d. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable).
 - e. Data set whose QT/QTc values are the average of the above replicates at each nominal time point.
13. Submit all related ECG waveforms to the ECG warehouse at www.ecgwarehouse.com.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Labeling issues and comments identified during our preliminary review of your submitted labeling are attached.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by January 26, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, the proposed package insert (PI), and the patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the PI and patient PI and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, please call Ms. Sharon Sickafuse, Senior Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:

Highlights of Clinical Pharmacology Table
Revised labeling

Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PATRICIA KEEGAN
11/28/2014

From: Sickafuse, Sharon
Sent: Wednesday, November 19, 2014 3:36 PM
To: Caster, Donna M (donna.caster@astrazeneca.com)
Cc: renee.wible2@astrazeneca.com
Subject: NDA 206995 - IR re CRO site inspection

Importance: High

Hi Donna,

My OSI reviewer has the following requests as she plans for an inspection of the Independent Radiology Review Vendor, CRO [REDACTED] (b) (4)

1. The sponsor provided efficacy endpoint data listings for each clinical site. It appears that these listings report the tumor response as determined by the clinical investigators at each site. Please submit the efficacy data listings as determined by the CRO, so that we can verify against source at the CRO site.
2. Please provide the Independent Radiology Review Charter for [REDACTED] (b) (4) so that we can confirm that the CRO performance was in accordance with not only the protocol but also the detailed Charter of exactly what and how they were to perform their IRR assessments.

If these items have already been submitted, please indicate where in the NDA that they are.

Thank you

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/s/

SHARON K SICKAFUSE
11/19/2014

From: Sickafuse, Sharon
Sent: Tuesday, November 18, 2014 5:24 PM
To: Caster, Donna M (donna.caster@astrazeneca.com)
Cc: renee.wible2@astrazeneca.com
Subject: NDA 206995 - ? re CRO site

Hi Donna,

Regarding your central review CRO site, [REDACTED]^{(b) (4)}, which physical location (Germany or UK) did you operate from and where are the records kept for the study?

Thanks

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/s/

SHARON K SICKAFUSE
11/19/2014

From: Sickafuse, Sharon
Sent: Friday, November 14, 2014 4:59 PM
To: Caster, Donna M (donna.caster@astrazeneca.com)
Cc: renee.wible2@astrazeneca.com
Subject: NDA 206995 - clinical IR

Hi Donna,

My clinical team has the following IR:

In study IFUM, 17 cases were “non-measurable” according to the IRC. Please describe, in detail, the sites of disease in these patients and any information from the IRC which would help explain the reason that these patients were “non-measurable.”

Please provide your response by December 20.

Thank you

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/s/

SHARON K SICKAFUSE
11/14/2014

From: Sickafuse, Sharon
Sent: Thursday, November 13, 2014 12:42 PM
To: Caster, Donna M (donna.caster@astrazeneca.com)
Cc: renee.wible2@astrazeneca.com
Subject: NDA 206995 - QT IR

Hi Donna,

Please submit all related ECG waveforms to the ECG warehouse at www.ecgwarehouse.com.

Thank you

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/s/

SHARON K SICKAFUSE
11/13/2014

From: Sickafuse, Sharon
Sent: Monday, November 10, 2014 1:22 PM
To: Caster, Donna M (donna.caster@astrazeneca.com)
Subject: NDA 206995 - QT IR
Attachments: Highlights_ClinPharm_and_Cardiac_Safety.doc

Hi Donna,

Please fill out the attached Highlights of Clinical Pharmacology Table and submit as an amendment to the NDA. My team is unable to locate the data for the QT study report. Please submit or provide the location of the following information:

- a. Annotated CRF.
- b. A data definition file which describes the contents of the electronic data sets.
- c. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses.
- d. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable).
- e. Data set whose QT/QTc values are the average of the above replicates at each nominal time point.

Thank you

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/s/

SHARON K SICKAFUSE
11/10/2014

From: Sickafuse, Sharon
Sent: Tuesday, November 04, 2014 11:25 AM
To: renee.wible2@astrazeneca.com
Subject: NDA 206995 - nonclinical IR

Hi Renee,

My nonclinical reviewer has the following IR:

Please submit a tabulated list of all nonclinical studies submitted to NDA 206995 that were not previously submitted to NDA 21399, and indicate where they are located within the submission.

Thank you

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/s/

SHARON K SICKAFUSE
11/04/2014

NDA 206995 Planning Meeting

Date: October 29, 2014

Product: Iressa (gefitinib)
Submission Date: September 17, 2014
Received Date: September 17, 2014
Sponsor: AstraZeneca

Proposed Indication: First-line treatment of patients with [REDACTED] (b) (4) metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutation(s) as detected by an FDA-approved test (Qiagen theascreen EGFR RGQ PCR kit).

Review Team/Collaborators for NDA 206995

Patricia Keegan, M.D., Director, DOP2
Sharon Sickafuse, M.S., Lead Regulatory Health Project Manager
Diko Kazandjian, M.D., Medical Officer
Gideon Blumenthal, M.D., Medical Officer (TL and CDTL)
Vivian Yuan, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Ruby Leong, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D., Clinical Pharmacology (TL)
Jerry (Jingyu) Yu, Ph.D., Pharmacometrics
Liang Zhao, Ph.D., Pharmacometrics (TL)
Robert Schuck, Ph.D. Genomics
Rosane Charlab Orbach, Ph.D., Genomics (TL)
Sachia Khasar, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Non-Clinical (TL)
Teicher Agosto, Product RPM
Joyce Crich, Ph.D., Product
Liang Zhou, Ph.D., Product (TL)
Robert Mello, Ph.D., Product Microbiology
Ali Al-Hakim, Ph.D., Product DD
Robert Wittorf, Ph.D., Facilities
Salah Hamed, Ph.D., Biopharmaceutics
Angela Dorantes, Ph.D., Biopharmaceutics (TL)
Frances Fahnbulleh, OSE RPM
Davis Mathew, OSE/DMEPA
Chi-Ming (Alice) Tu, OSE/DMEPA (TL)
Mona Patel, Pharm D, OSE/DRISK
Naomi Redd, OSE/DRISK (TL)
Lauren Iacono-Connor, OSI
Olga Salis, OPDP RPM

Nazia Fatima, OPDB
 Barbara Fuller, Patient Labeling (TL)
 Jennifer Shen, CDRH

Review Status:

- Priority review requested, but denied. This NDA will receive standard review and be on a 10 month clock.
- Categorical Exclusion requested
- Has Orphan Drug designation, so PREA doesn't apply.
- Qiagen submitted a PMA amendment for *therascreen EGFR* RGQ PCR kit to include Iressa as a treatment option for patients with EGFR mutation-positive tumors.

1. Dates for Milestones and for When Letters Must Issue:

Milestone	Due
Acknowledgment Letter	Issued 9-29-2014
Deficiencies Identified Letter (74 Day Letter) Sent comments to RPM by 11-19-2014. Letter will include comments on PI.	11-28-2014
Send proposed labeling/PMR/PMC/REMS to applicant	5-29-2015
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	5-22-2015 5-29-2015 6-5-2015 6-26-2015 7-17-2015
Compile and circulate Action Letter and Action Package	6-5-2015
FINAL Action Letter Due	7-17-2015

2. Consults/Collaborative Reviewers:

OPDP	Olga Salis – RPM Nazia Fatima
------	----------------------------------

OSE	Frances Fahnbulleh - OSE RPM Mona Patel - DRISK Davis Mathew - DMEPA
OSI	Lauren Iacono-Connor assigned, site selection in progress.
Pediatric Record/PeRC	Pediatric Record completed in DARRTS.
QT-IRT consult	Sent 10-29-2014
SGEs or Patient Representatives	Not needed
Patient labeling	Nathan Caulk

3. Upcoming Internal Team Meetings:

Planning Meeting held on: October 29, 2014

Filing Meeting scheduled for: November 10, 2014

Signed filing reviews due November 14, 2014.

[Applicant Orientation Presentation: November 14, 2014]

Team Meeting scheduled for: December 22, 2014

Mid-Cycle Meeting scheduled for: February 17, 2015

TBA:

Labeling meetings

PMR/PMC meeting, if needed

Wrap-up Meeting

4. Will we do an ODAC presentation? No

5. At this time, no one identified any filing issues.

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/s/

SHARON K SICKAFUSE
10/29/2014

From: Sickafuse, Sharon
Sent: Thursday, October 09, 2014 1:24 PM
To: renee.wible2@astrazeneca.com
Subject: NDA 206995 clinical site IR

Hi Renee,

My team has the following IR:

The Office of Scientific Investigations (OSI) is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. The IFUM (D791AC00014) study provides data for the efficacy and safety of gefitinib in the first-line treatment of patients with aNSCLC whose tumors have EGFR Exon 19 deletions or the Exon 21 substitution (L858R) mutation. We request that you consider providing datasets specifically for the IFUM study for use in our Risk Based Site Selection tool.

Please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Thank you

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/s/

SHARON K SICKAFUSE
10/09/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 9, 2014

From: Patricia Keegan, M.D., Director, Division of Oncology Products 2

Subject: Designation of Review Schedule for NDA Review
Sponsor: AstraZeneca Pharmaceuticals LP
Product: Iressa (gefitinib)
Indication: First line treatment of patients with [REDACTED] (b) (4)
metastatic non-small cell lung cancer whose tumors have
epidermal growth factor receptor (EGFR) exon 19 deletion or
exon 21 (L858R) substitution mutations as detected by an FDA-
approved test

To: NDA 206995

The review status of this NDA is designated to be:

Standard (10 mon.)

Priority (6 mon.)

Summary of Applicant's Request for Priority Designation

AstraZeneca has requested priority review for this NDA. Demonstration of efficacy relies on the results of a single-arm, multicenter trial (IFUM), with supportive evidence obtained from retrospective analyses in convenience samples (those with available tumor specimens for re-testing) in a randomized clinical trial (IPASS). The IFUM trial evaluated the antitumor activity (response rate), safety and tolerability of gefitinib 250 mg per day as a first-line treatment of 106 patients with EGFR mutation-positive, locally advanced or metastatic NSCLC. The trial demonstrated an objective response rate of 69.8% (95% CI: 60.5-77.7%) and a median duration of response of 8.3 months.

IPASS was an open-label, multicenter, randomized (1:1), trial designed to establish that gefitinib treatment was non-inferior to carboplatin/paclitaxel doublet chemotherapy with regard to survival. The trial enrolled 1217 patients receiving first-line treatment for Stage IIIB or Stage IV adenocarcinoma of the lung; the trial was "enriched" for patients likely to have EGFR mutations, i.e., all patients were Asian and had never smoked or were light ex-smokers. The trial failed to demonstrate non-inferiority in survival, however in subgroup analysis, patients with EGFR-mutation positive NSCLC randomized to gefinitib had higher response rates (71% vs. 47%) and progression-free survival (HR 0.48 (95% CI 0.36, 0.64), with a nominally significant p-value.

As justification for priority designation, AstraZeneca states "Gefitinib would provide a well-tolerated and effective targeted therapy for the first-line treatment of adult patients with EGFR mutation-positive aNSCLC, a disease setting where treatment options are still needed."

Astra Zeneca also states that "There is now a large body of evidence demonstrating consistent efficacy of EGFR TKIs (gefitinib, erlotinib, afatinib) in patients with sensitizing *EGFR*

mutations, regardless of ethnicity, and that these patients are more likely to benefit from initial treatment with an EGFR TKI in preference to doublet chemotherapy (Douillard et al 2014 [IFUM study], Maemondo et al 2010, Mitsudomi et al 2010, Mok et al 2009 [IPASS study], Rosell et al 2012, Sequist et al 2013, Zhou et al 2011). Erlotinib and afatinib are considered to be in the same pharmacological class as gefitinib.”

Finally, AstraZeneca states that “Data that prospectively compare the efficacy/effectiveness and tolerability of gefitinib with other EGFR TKIs are not available at the current time. However, based on the data reported from randomised Phase III trials versus chemotherapy, it is clear that the efficacy observed with each of the EGFR TKIs is similar but that each drug has a different tolerability and safety profile.”

Review Designation:

I am designating this application as a standard review based on failure to meet the criteria specified in FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014) and for the reasons discussed below.

An application will be given priority review designation if it meets any of the following criteria:

- An application (original or efficacy supplement) for a drug that treats a serious condition **AND**, if approved, would provide a significant improvement in safety or effectiveness
- Any supplement that proposes a labeling change pursuant to a report on a pediatric study under 505A
- An application for a drug that has been designated as a qualified infectious disease product
- Any application or supplement for a drug submitted with a priority review voucher

The NDA submitted by AstraZeneca does not meet the criteria under bullets 2-4 above. While the application is for a drug that treats a serious condition (EGFR mutation-positive, (b) (4) metastatic non-small cell lung cancer), the justification provided does not support a conclusion that if approved, it would provide a significant improvement in safety or effective over available therapy, i.e., erlotinib or afatinib. As described in the Guidance, examples of significant improvement include

- Evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition
- Elimination or substantial reduction of a treatment-limiting adverse reaction
- Documented enhancement of patient compliance that is expected to lead to an improvement in serious outcomes
- Evidence of safety and effectiveness in a new subpopulation

AstraZeneca’s argument for significant improvement relies on bullet 2 above (elimination or substantial reduction of a treatment-limiting adverse reaction). However, the application does not provide adequate data to support this argument. First, there were no trials submitted in the application that provided a direct comparison of the safety and effectiveness of gefitinib to erlotinib or afatinib. Second, AstraZeneca does not identify a specific treatment-limiting adverse reaction upon which this argument rests. On inspection of the summary data in the NDA and product labeling for erlotinib and afatinib, the serious and potentially treatment-limiting adverse reactions of interstitial lung disease and cutaneous toxicity are observed with all three drugs; cross-study comparisons do not allow a clear determination that true differences exist.

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/s/

PATRICIA KEEGAN
10/09/2014



NDA 206995

NDA ACKNOWLEDGMENT

AstraZeneca UK Limited
Attention: Mark DeSiato
Senior Director, Global Regulatory Affairs
AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. DeSiato:

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

Name of Drug Product: IRESSA (gefitinib) 250 mg tablets

Date of Application: September 17, 2014

Date of Receipt: September 17, 2014

Our Reference Number: NDA 206995

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 16, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

SHARON K SICKAFUSE
09/29/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

preIND 120992

MEETING MINUTES

AstraZeneca LP
Renee Wible
Senior Director, Global Regulatory Affairs
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850

Dear Ms. Wible:

Please refer to your Pre-Investigational New Drug Application (preIND) file for "Iressa (gefitinib)."

We also refer to the meeting between representatives of your firm and the FDA on March 11, 2014. The purpose of the meeting was to discuss a proposed New Drug Application (NDA) for Iressa for the first-line treatment of patients with (b) (4) metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 substitution mutations as detected by an FDA-approved test.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-2320.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: preIND/preNDA
Meeting Date: March 14, 2014
Application Number: preIND 120992
Product Name: Iressa (gefitinib)
Indication: First-line treatment of patients with (b) (4) metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 substitution mutations as detected by an FDA-approved test
Sponsor/Applicant Name: AstraZeneca LP (AZ)
Meeting Chair: Gideon Blumenthal
Meeting Recorder: Sharon Sickafuse

FDA ATTENDEES

**Center for Drug Evaluation and Research
Office of Hematology and Oncology Products**

Jonathan Jarow, MD.
Richard Pazdur, M.D.

Division of Oncology Products 2
Gideon Blumenthal, M.D.
Patricia Keegan, M.D.
Sharon Sickafuse, M.S.

Division of Hematology Oncology Toxicology
Emily Fox, Ph.D.
Whitney Helms, Ph.D.

Office of Clinical Pharmacology

Division V
Walt Cao, Ph.D.
Nam Atiqur Rahman, Ph.D.
Hong Zhao, Ph.D.

Type B

Office of Biostatistics

Division V

Shenghui Tang, Ph.D.

Office of Surveillance and Epidemiology

Division of Risk Management

Amarilys Vega

Center for Devices and Radiological Health

Office of In Vitro Diagnostics and Radiological Health

Division of Immunology and Hematology Devices

Jennifer Shen, Ph.D.

SPONSOR ATTENDEES

Antoine Yver, MD, MSc, Vice President, Global Medicine Development, Oncology

Hesham Abdullah, MD, MSc, RAC, Vice President, Global Regulatory Affairs, Oncology

Maxwell Kirkby, BSc, MRPharmS, Global Product Vice President, Oncology

Haiyi Jiang, MD, MSc, Medical Science Director, Oncology

Alan Webster, MSc, Global Product Statistician

Weifeng Tang, PhD, Senior Clinical Pharmacology Scientist

Jill Walker, MD, Director, Companion Diagnostic Development

Renée Wible, RN, BSN, Senior Director, Global Regulatory Affairs, Oncology

Cindy Lancaster, MS, MDA, JD, Senior Director, Global Regulatory Affairs Policy

Nick Botwood, MD, Clinical Vice President Oncology, Global Medicines Development

BACKGROUND

On December 24, 2013, AstraZeneca (AZ) submitted a meeting request to discuss the content and format of a New Drug Application (NDA), which would adequately support characterization of the risk/benefit of IRESSA as a first-line treatment of patients with epidermal growth factor receptor (EGFR) mutation positive (exon 19 deletions and exon 21 L858R point mutations) (b) (4) metastatic non-small cell lung cancer (NSCLC).

On May 5, 2003, NDA 21399 for IRESSA was approved under the provisions of 21CFR 314, subpart H for the following indication:

IRESSA is indicated as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies.

The effectiveness of IRESSA is based on objective response rates (see CLINICAL PHARMACOLOGY-Clinical Studies section). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Type B

Results from two large, controlled, randomized trials in first-line treatment of non-small cell lung cancer showed no benefit from adding IRESSA to doublet, platinum-based chemotherapy. Therefore, IRESSA is not indicated for use in this setting.

Following accelerated approval, AZ initiated three confirmatory Phase 3 studies. The IBREESE study was closed early. AZ claims that the INTEREST study, for second-line unselected patients, showed non-inferiority compared to docetaxel in the primary endpoint of overall survival (OS). However, the ISEL study failed to show improvement over placebo for second- and third-line NSCLC patients.

In June 2005, following results of a double-blind, placebo-controlled parallel-group trial in 1692 patients with advanced NSCLC randomized to receive either IRESSA or best supportive care, in which no improvement in OS was demonstrated, the approved indication for IRESSA was revised as follows:

IRESSA is indicated as monotherapy for the continued treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies who are benefiting or have benefited from IRESSA.

In light of positive survival data with other agents including another oral EGFR inhibitor, physicians should use other treatment options in advanced non-small cell lung cancer patient populations who have received one or two prior chemotherapy regimens and are refractory or intolerant to their most recent regimen.

IRESSA was voluntarily withdrawn from the U.S. market on April 25, 2012 (date of Federal Register Notice). All patients who were under treatment with IRESSA were allowed to continue treatment under an intermediate-size expanded access protocol

Using data from ISEL and other studies, AZ determined that the clinical features of adenocarcinoma histology, Asian ethnicity, and females who never smoked were important in response to gefitinib and subsequently it was found that these clinical characteristics were surrogates for EGFR activating mutations. IPASS was designed to select patients based on the clinical surrogate of never/light smokers with exploratory EGFR testing. In 2008, AZ announced that the completed study met its primary endpoint of improved progression-free survival (PFS). Subsequently, AZ conducted the IFUM study as a post-marketing commitment for the European Medical Agency to confirm benefit in Caucasian patients.

Study IFUM

Study IFUM was a multicenter, single-arm study intended to characterize the efficacy and safety of gefitinib 250 mg (once daily) as first-line treatment in Caucasian patients with EGFR mutation-positive, locally advanced or metastatic NSCLC. Patients with T790M, exon 20 insertions, or S768I mutations were excluded. The primary endpoint was overall response rate (ORR) as assessed by the investigator.

Type B

The EGFR RCQ PCR kit (Qiagen) was used to perform the EGFR mutation analysis on patient samples to select eligible patients for enrollment into the IFUM study. This platform assays 29 mutations across EGFR Exons 18-21.

A total of 106 patients were enrolled. The most common mutation in tumor samples at baseline was Exon 19 deletion (69 patients), followed by L859R (33 patients), L861Q (2 patients), and G719X (2 patients).

AZ states that IFUM met its primary objective, demonstrating an ORR of 69.8% (95% CI: 60.5% to 77.7%). An independent review determined an ORR of 50%.

Regarding the safety profile, AZ states that rash was the most frequently reported adverse event (44.9% of patients), followed by diarrhea (30.8%), vomiting (13.1%), asthenia, cough and dry skin (11.2% each), and nausea (10.3%).

Study IPASS

Study IPASS study was an open label, multicenter, randomized study comparing PFS between patients randomized to gefitinib with those randomized to carboplatin plus paclitaxel chemotherapy in the first-line treatment of patients from Asian countries with Stage IIIB or Stage IV adenocarcinoma of the lung who never smoked or were light ex-smokers. Tumor assessment was performed every 6 weeks until progressive disease.

A total of 1217 patients were enrolled. AZ notes that study IPASS met its primary endpoint of demonstration of an improvement in PFS in the intent-to-treat (ITT) population, with a PFS HR was 0.74 (95% CI: 0.65, 0.85). Retrospective data collection for EGFR mutation status and for blinded, independent, central review of tumor-based endpoints was conducted by AZ.

The ability of data from IPASS to support an sNDA was discussed during a December 2009 meeting with AZ. FDA noted that the PFS analysis reported for the ITT population for this open-label study was not confirmed by independent review and that there was no evidence available for effects on OS, particularly in light of multiple prior negative trials and given that the IPASS trial was conducted entirely outside the US. During the meeting, FDA agreed that a subgroup analysis of PFS as determined by an independent review committee in patients with EGFR mutation-positive NSCLC as determined by an analytically validated test could be considered for review. In addition, AZ would need to provide justification for extrapolation of the data to the US population.

In the meeting package for the March 2014 meeting, AZ stated that tumor samples were available for testing for analysis of EGFR mutation status in 56% of the trial population and in 36% (n=437) of the trial population, EGFR mutation status could be determined using the commercially available DxS EGFR 29 mutation kit. Of the 437 patients with information on EGFR mutation status, a total of 261 patients' tumors were classified as EGFR mutation positive (132 in the gefitinib arm and 129 in the control arm) and 176 were classified as EGFR mutation negative. As stated in the meeting package, AZ has obtained

Type B

scans for approximately 75% (approximately 200 patients, which is approximately 15% of the trial population) of the subset of patients with EGFR mutation-positive tumors.

In the subset of patients identified as having EGFR mutation-positive NSCLC (n= 261), the PFS HR was 0.48 (95% CI 0.36, 0.64), with an increase in median PFS of 3.2 months for the gefitinib group. There was no evidence of an improvement in the key secondary endpoint of OS in the subgroup of patients identified as having EGFR mutation-positive NSCLC, with a HR for OS of 1.00 (95% CI: 0.76, 1.33).

AZ claims that toxicity was better with gefitinib compared to platinum doublet chemotherapy. Common adverse events (AEs) included rash, dry skin, paronychia, nail and nail bed conditions, diarrhea, stomatitis, pruritus, and transaminase elevation. Grade ≥ 3 AEs included ALT increase, diarrhea, and abnormal hepatic function.

Supportive Clinical Data

AZ proposes to submit the following additional information to establish the safety and efficacy of IRESSA:

- The clinical study report prepared by the West of Japan Oncology Group (WJOG), without case report forms or datasets for Protocol WJTOG3405 and publications describing the results of studies NEJ001, NEJ002, NEJ003, and iTARGET. Studies WJTOG3405 and NEJ002, which were randomized, multicenter, trials conducted in Japan, enrolled 172 and 228 patients, respectively. Both studies enrolled patients whose tumors harbored EGFR mutations, investigated gefitinib 250 mg daily dose, and were conducted in patients receiving initial treatment for NSCLC, comparing gefitinib to platinum doublet therapy. AZ claims that both studies showed clinically important and statistically significant improvements in PFS.
- Safety and tolerability data from the world-wide marketing experience. AZ estimates that a total of 76,000 patients have been exposed to gefitinib. The most common AEs are skin toxicity and diarrhea while the most serious AEs are interstitial lung disease and hepatitis.

Companion Diagnostic

Concurrent with the submission of the proposed NDA, Qiagen will submit an amendment to their PMA for the *therascreen*[®] EGFR RCQ PCR test to include use for selection of patients with NSCLC for whom gefitinib is indication. In order to support this PMA amendment and label expansion, Qiagen will conduct and provide the results of a bridging study between the clinical trial assay used to select patients for enrollment in the IFUM trial (EGFR RCQ PCR kit (Qiagen)) and the FDA-approved, *therascreen*[®] EGFR RCQ PCR test, using tumor samples from approximately 98% (n=818) of the 859 patients with known mutation status who were screened for enrollment in the IFUM trial. Qiagen and AZ will discuss with CDRH the design of the bridging study prior to its conduct.

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Preliminary comments were emailed to AZ on March 7, 2014. AZ replied by email on March 10, 2014, and said that they would like to discuss question #5 and provide their plans for addressing FDA comments #19, 20, 22, and 23 and gain agreement on their proposal

PREAMBLE

In their meeting package, AZ proposes to include the following efficacy datasets in the planned NDA submission:

1. Efficacy data for the subset of patients enrolled in the Study IPASS who were determined to be EGFR-mutation-positive on a retrospective analysis, constituting approximately 20% of the 1217 patients registered and randomized in this clinical trial.
2. Efficacy data for all patients enrolled in Study IFUM, a single arm study conducted in patients with EGFR mutation-positive NSCLC.

FDA considers the efficacy results and independent confirmation of objective response rate (ORR) and duration in the IFUM study as the primary data to be reviewed in support of the benefit-risk assessment in the NDA submission. FDA considers the retrospective analysis in the convenience subset of IPASS to be supportive.

In the NDA submission, AZ should provide justification for why independently confirmed ORR and duration of response results from IFUM should be considered as a measure of direct clinical benefit in the context of results from other drugs in this class tested in this patient population.

FDA will also consider supportive data from IPASS and the published results from two randomized trials conducted prospectively in Japanese patients with EGFR mutation-positive NSCLC (NEJ002 and WJTOG3405) for which AZ does not intend to provide datasets. Should AZ wish to make comparative claims of efficacy versus doublet chemotherapy in the proposed patient population, FDA recommends that the datasets from studies NEJ002 and WJTOG3405 be submitted with the NDA. AZ should provide further explanation for the inability to provide datasets and CRFs for studies WJTOG3405 and NEJ002, or if possible, should also submit datasets and CRFs for these two Japanese studies. If submitted, the format should follow the CDISC Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) standards as described below.

SPONSOR QUESTIONS AND FDA RESPONSE

Clinical

1. *AstraZeneca (AZ) considers that efficacy and safety data from two pivotal studies, IFUM and IPASS, together with supportive information from the West of Japan Oncology Group trial (WJTOG3405; CSR prepared by WJOG, without CRFs or datasets), and supportive information from studies NEJ001, NEJ002, NEJ003 and iTARGET (to be*

Type B

provided as publications), is appropriate to characterise the risk-benefit of gefitinib in patients with epidermal growth factor receptor (EGFR) mutation-positive (exon 19 deletions and exon 21 L858R point mutations) locally advanced or metastatic non-small cell lung cancer (EGFR mutation positive NSCLC). Specifically, AZ considers that this data package would properly form the basis of a marketing application and support the indication for use of gefitinib as first-line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) with exon 19 deletions or exon 21 (L858R) substitution epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test. Does the Agency agree?

FDA Response:

Yes, as per the preamble, FDA agrees that independently confirmed results from IFUM could form the basis of a marketing application and allow a benefit-risk assessment to support a proposed indication for gefitinib as first line treatment of patients with metastatic NSCLC containing an EGFR exon 19 deletion or exon 21 (L858R) substitution as detected by an FDA-approved test. The results of IPASS, NEJ002, and WJTOG would be considered supportive data.

With respect to the IPASS and IFUM studies, FDA recommends that sensitivity analyses be conducted investigating ORR, PFS, and OS by specific EGFR mutation type. Furthermore, given IPASS' retrospective analysis of EGFR mutation type, an analysis excluding resistant mutations (e.g., T790M, exon 20 insertions) should be conducted.

Discussion:

AZ did not have any questions or comments.

- AZ proposes to conduct a retrospective independent review of the scans from patients with EGFR mutation positive tumours in IPASS to verify the consistency of the magnitude of PFS effect observed in support of the proposed indication (scans will be available upon request). Does the Agency agree?*

FDA Response:

It is acceptable to have a blinded independent review of scans only from the subset of patients retrospectively identified as having EGFR mutation-positive NSCLC. However, please note that the available scans (~75%) for this subgroup are not randomly sampled from the EGFR mutation-positive population. Data from a convenience sample could introduce selection bias in subgroup analyses.

Discussion:

AZ did not have any questions or comments.

- The safety profile of IRESSA is well characterised from 10 years of market experience. As of July 5, 2013, the cumulative exposure to gefitinib in clinical studies is estimated at more than 76,000 patients, and the total cumulative market exposure to gefitinib is estimated at more than 186,500 patient-years. AZ considers the safety profile of gefitinib*

Type B

in NSCLC patients who are EGFR mutation positive to be in line with the safety profile of gefitinib in the general population of NSCLC patients. Does the Agency agree that the totality of the safety data from IPASS and IFUM together with the latest Periodic Benefit-Risk Evaluation Report (PBRER; covering July 6, 2012 - July 5, 2013) and the subsequent PBRER (covering July 6, 2013 - July 5, 2014, planned for submission in September 2014) would be appropriate to characterize gefitinib safety and tolerability in the US population and are sufficient to support the proposed indication?

FDA Response:

Yes, FDA in general agrees with this plan of submitting safety data, including the PBRER which will summarize the gefitinib safety experience, pending the quality and integrity of the data submitted.

Discussion:

AZ did not have any questions or comments.

4. *AZ proposes to provide both electronic and written patient narratives for patients who experienced a fatal AE, a serious AE, discontinuation from study treatment due to an AE, a significant AE or death due to disease progression from the two pivotal studies of IPASS and IFUM. Does the Agency agree?*

FDA Response:

Yes, FDA agrees with the plan of submitting patient narratives as outlined in section 5.6 of the meeting package.

Discussion:

AZ did not have any questions or comments.

5. *Does the Agency agree with the proposal for meeting the requirements of the Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety (ISS) in the NDA?*

FDA Response:

Yes, FDA agrees with the proposal outlined in the meeting package. Namely, for the submission of an ISE and ISS split between modules 2 and 5, for text and for protocols and datasets, respectively.

For the ISE, in addition to the information proposed, also provide a pooled analysis of ORR and duration of response (DoR) by specific mutation (i.e., exon 19 deletion, exon 21 L858R substitution, and other specific mutations).

For the ISS, FDA suggests both independent and pooled analysis of safety data from studies to identify rare but clinically significant adverse reactions (i.e. pneumonitis, liver failure). Additional analyses should include pooled analyses of placebo controlled studies separate from pooled active control studies.

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As noted in the meeting package, these should be in a format consistent with the FDA Guidance For Industry which can be found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf> and <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>.

Discussion:

AZ stated that for the ISE, they will pool data from Studies IPASS and IFUM in order to evaluate ORR and DoR by EGFR mutation subtype. FDA stated that this is acceptable.

FDA stated that for common adverse events, data from the placebo-controlled, randomized trial, ISEL, would be useful to inform product labeling. AZ agreed to provide this data in tabular format. FDA agreed that the dataset would not have to be reformatted into CDISC.

AZ stated that for the ISS, they do not plan to perform a pooled analysis of safety data from clinical trials conducted in the unselected patient population. This approach is acceptable to FDA. AZ will provide a side by side comparison of safety data from study IFUM, study IPASS all patients, and study IPASS EGFR mutation positive patients.

6. *AZ proposes that data from the two pivotal studies, IPASS and IFUM, will be submitted using CDISC Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) standards. A clinical study report (CSR) will be submitted for the WJTOG3405 trial. CSRs for AZ studies conducted in unselected patient populations prior to IPASS will also be submitted. Does the Agency agree with the proposed content/format for the individual study datasets?*

FDA Response:

Yes, FDA agrees with submitting data in the CDISC and SDTM standards as outlined in section 5.10 of the meeting package. Furthermore, please submit summarized “one patient per row” efficacy data and demographics for IPASS and IFUM. If AZ is also able to obtain datasets from studies WJTOG3405 and NEJ002, please describe the content/format of these studies.

Discussion:

AZ did not have any questions or comments.

7. *Does the Agency agree that the proposed Table of Contents is appropriate and sufficient to support review of the NDA?*

FDA Response:

The table of contents appears incomplete. Please see the Office of Scientific Investigations’ requirements which are attached. In addition, the table of contents does

Type B

not list any pharmacology data that is planned for submission to the NDA. Please include all pharmacology studies that AZ wishes to use to support claims for the mechanism of gefitinib in the currently proposed indication.

A detailed guidance on the format can be found at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163175.pdf>.

Discussion:

AZ did not have any questions or comments.

Clinical Pharmacology

8. *AZ intends to submit a comprehensive Biopharmaceutics and Clinical Pharmacology package in Clinical Summary Modules 2.7.1 and 2.7.2, including 30 studies that provided clinical pharmacokinetics and pharmacokinetic/pharmacodynamic relationship information. These studies were performed in healthy volunteers or patients. For all of these studies, AstraZeneca intends to submit the clinical study report and TLFs (Tables, Listings, Figures). In addition, for the IFUM study, AstraZeneca intends to provide the population PK analysis report, dataset and specification, and control stream. Does the Agency agree with this approach?*

FDA Response:

The clinical pharmacology plan appears acceptable. See additional clinical pharmacology comments below.

Discussion:

AZ did not have any questions or comments.

Companion Diagnostic

9. *AstraZeneca proposes to work with a diagnostic partner (QIAGEN) to submit a PMA amendment, closely in parallel to the NDA submission,*

(b) (4)

(b) (4)

(b) (4) Does the Agency agree?

FDA Response:

(b) (4)

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(b) (4)

Discussion:

AZ did not have any questions or comments.

ADDITIONAL FDA COMMENT:

10. Please submit a proprietary name for review by the Division of Medication Error Prevention and Analysis if AZ intends to have one for this product. See the FDA Guidance for Industry, "Contents of a Complete Submission for the Evaluation of Proprietary Names," available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

Discussion:

AZ did not have any questions or comments.

ADDITIONAL FDA CLINICAL PHARMACOLOGY COMMENTS;

Please address the following clinical pharmacology related questions in the NDA submission:

11. What is the basis for selecting the dose(s) and dosing regimen used in the registration trial(s)?
12. What are the exposure-response relationships (dose-response, exposure-response) for efficacy?
13. What are the exposure-response relationships (dose-response, exposure-response) for safety?
14. How is the QT prolongation potential of gefitinib assessed? What is the conclusion and proposed labeling description?
15. What are the characteristics of absorption, distribution, metabolism and excretion of gefitinib?
16. What are the effects of food on the bioavailability of gefitinib and the dosing recommendation(s) with regard to meals or meal types?
17. What influence do the intrinsic factors (as listed below, but not limited to) have on gefitinib exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
 - a. gender

Type B

- b. race
- c. weight
- d. disease
- e. genetic polymorphism
- f. hepatic impairment
- g. renal impairment

18. What influence do the extrinsic factors (as listed below, but not limited to) have on gefitinib exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
- a. concomitant medications
 - b. CYP and/or transporter based drug-drug interactions
 - c. diet
 - d. smoking

Discussion regarding items #11-18:

AZ did not have any questions or comments.

Please apply the following advice in preparing clinical pharmacology sections of the NDA submission:

19. Submit bioanalytical method(s) and validation reports for clinical pharmacology and biopharmaceutics studies.

Discussion:

AZ did not have any questions or comments.

20. Provide complete datasets for clinical pharmacology and biopharmaceutics studies. The datasets should not be limited to PK/PD. For example, domains related to safety (e.g., AEs), demographics, non-PK laboratory values, and concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes and facilitating exploratory exposure-response analyses and population PK analyses.

Discussion:

FDA stated that AZ will need to resubmit the clinical study reports for clinical pharmacology studies contained in NDA 21399. Any data to support new labeling will need to be submitted in detail for full review.

21. Provide all concentration-time and derived PK parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Type B

Discussion:

AZ's proposed to submit data from studies previously submitted in NDA 21399 in PDF format with tabular listings and figures. FDA stated that this approach is acceptable.

22. Present the PK parameter data as geometric mean with coefficient of variation (and mean \pm standard deviation) and median with range as appropriate in the study reports.

Discussion:

AZ did not have any questions or comments.

23. Provide a table listing of patients with renal or hepatic impairment who have received gefitinib, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation and/or eGFR calculated by MDRD, AST/ALT, total bilirubin, etc. for each patient in the listing. Also, provide a summary of the following information for each patient: PK and PD data, safety, and clinical efficacy.

Discussion:

AZ will provide data and a justification to support their position that no renal impairment studies are necessary. AZ will submit data from two hepatic impairment studies that provide information on PK, PD, safety, and efficacy. FDA stated that this approach is acceptable.

FDA requested that AZ provide all available data on gefitinib administration in renal impaired patients. AZ agreed to do so.

24. Submit the following datasets to support the population PK analysis:
- a. SAS transport files (*.xpt) for all datasets used for model development and validation.
 - b. Description of each data item provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - c. Model codes or control streams and output listings for all major model building steps e.g., base structural model, covariates models, final model, and validation model. Submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).
 - d. Model development decision tree and/or table which gives an overview of modeling steps.

Type B

Discussion:

AZ will submit a complete report and datasets for population PK analyses in the IFUM study only. They have performed a total of six population PK analyses and will provide study reports only for the earlier population PK analyses submitted to the withdrawn NDA. FDA stated that this is acceptable and may request additional information as needed.

25. For the population analysis reports, submit:
- a. Standard model diagnostic plots
 - b. Individual plots for a representative number of subjects including observed concentrations, the individual prediction line and the population prediction line.
 - c. Model parameter names and units in tables. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1).
 - d. Summary of the report describing the clinical application of modeling results. Refer to the pharmacometric data and models submission guidelines at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm> for more information.
 - g. Explore exposure-response (measures of effectiveness, biomarkers and toxicity) relationships for gefitinib and its major active metabolite(s) in the targeted patient population and include the results of this exploratory analysis in the NDA submission. Refer to FDA Guidance for Industry found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> and <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf> for more information.

Discussion:

AZ did not have any questions or comments.

ADDITIONAL DISCUSSION ITEM:

26. FDA recommended that AZ submit an IND amendment describing all differences in CMC and facilities between NDA 21399 and the proposed NDA. AZ agreed to do so and stated that they plan to submit the NDA in August.
-

Type B

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

(b) (4)

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements of Prescribing Information* website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents, and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Type B

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit a proprietary name for review by the Division of Medication Error Prevention and Analysis if AZ intends to have one for this product.	AZ	TBD
Submit an IND amendment describing all differences in CMC and facilities between NDA 21399 and the proposed NDA.	AZ	TBD

ATTACHMENTS

Office of Scientific Investigations (OSI) Requirements

OHOP's End-of-Phase 2 General Advice for Planned Marketing Applications

Type B

Office of Scientific Investigations Requirements

OSI requests that the items in Attachment 1 be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., Phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe the location or provide a link to the requested information. Site-specific individual data listings for the pivotal study may be submitted prior to the submission of the NDA, but no later than the final component, of the NDA, for all clinical study sites that enrolled subjects in the pivotal study. Provision of complete information as requested in Parts I and II will facilitate, and more importantly accelerate, development of clinical investigator and sponsor/monitor/CRO inspection assignments and the preparation of the inspection-supporting background packages. In order for the application to be considered complete at submission, it should contain elements that fully address Part I (General Study Related Information and Comprehensive Clinical Investigator Information) and Part II (Subject Level Data Listings by Site) of the OSI Pre-NDA/NDA Request (See Attachment 1).

Attachment 2 provides instructions for where all OSI requested items should be placed within an eCTD submission.

Office of Scientific Investigations Attachment 1

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

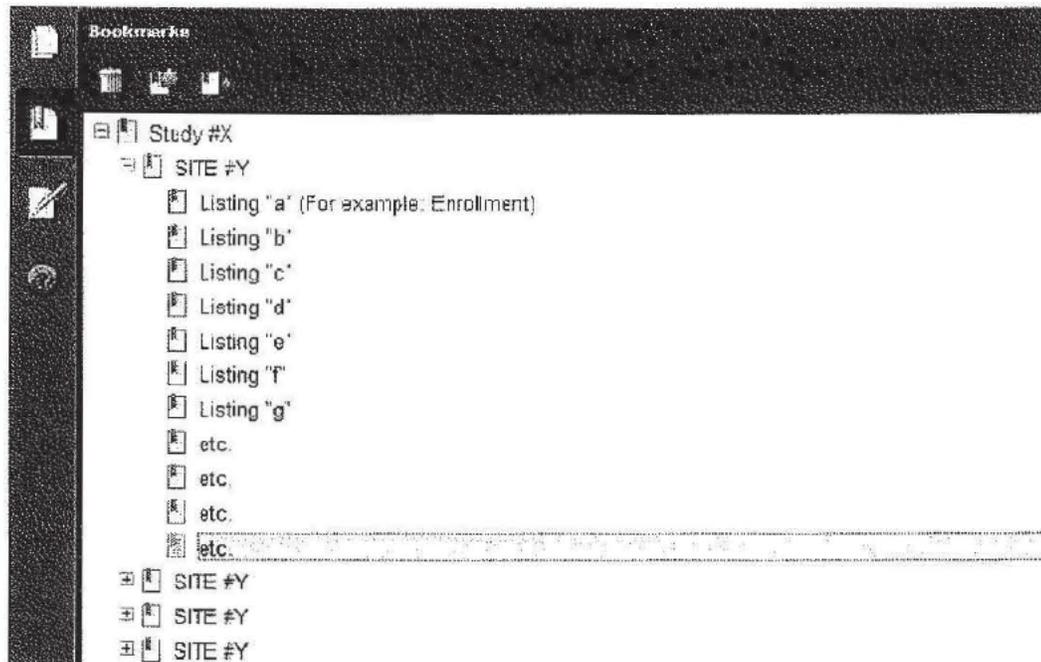
Type B

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:

Type B



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Office of Scientific Investigations Attachment 2

Technical Instructions:

Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

OSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

```

├─ [m5]
│   └─ datasets
│       └─ bimo
│           └─ site-level

```

- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

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Office of Hematology and Oncology Products
Division of Oncology Products 2

Type B

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

OHOP's End-of-Phase 2 General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

FDA's methodology and submission structure for regulatory applications supports research study design, as indicated in the *Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* and the *Study Data Specifications*. Our methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. Each study should be complete and evaluated on its own merits. The sponsor/applicant should maintain study data independently in the SEND datasets for non-clinical tabulations, SDTM datasets for clinical tabulations, and ADaM datasets for analyses tabulations. (See *SEND*, *SDTM* and *ADaM* as referenced in *Study Data Specifications*). Study analyses datasets should be traceable to the tabulations datasets.

The *PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017* guidance provides specific requirements for electronic submissions and standardization of electronic drug application data. Sponsors/Applicants should design and implement data standardization in all research protocols to be included in regulatory submissions, as required, based on the timing for implementation of the research. The non-clinical and clinical research study designs should include concise and complete explanation for implementation of data standardization in the data collection section of the protocol. The sponsor/applicant should use the Clinical Data Interchange Standards Consortium (CDISC) Technical Road Map to design end-to-end harmonized data standardization, including the Clinical Data Acquisition Standards Harmonization (*CDASH*) standard for design and implementation of data collection instruments.

The *Study Data Specifications* provide the current specifications for submissions. The specifications provide the most conducive data content definition and structure for the review team. The review team assigned to the submission determines the acceptability. Therefore, you are encouraged to follow this best practice noted in the *Study Data Specifications*, "prior to submission, sponsors should discuss with the review division the datasets that should be provided, the data elements that should be included in each dataset and the organization of the data within the file".

In addition, please reference the *CDER Common Data Standards Issues Document* for further information on data standardization in submissions. The purpose of the document is to highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant regarding submission of CDISC data in support of an application for

Type B

registration. In addition to the information and guidance provided at the above FDA link and CDISC links contained therein, the Division Oncology Products 2 (DOP2) has attached a separate document that details additional Oncology Specific domains and variables that we request be used for all oncology submissions. These domains and variable specifications have been developed by CDISC and will be included in the implementation guidance in the near future. DOP2 is using these domains

Additional Links:

[Electronic Regulatory Submissions and Review Helpful Links](#)
[Electronic Common Technical Document \(eCTD\)](#)

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application. These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application, we encourage you to provide justification and discuss it with us.

GENERAL
Special Protocol Assessment (SPA) Requests
1) It is strongly recommended that you discuss protocols for SPA request at an EOP2 meeting. The SPA protocol should be limited to one indication. Discussions of other indications may warrant another meeting. In addition, the Agency may agree that a specific finding (e.g., a particular p-value on the primary efficacy endpoint) of a study will satisfy a specific objective (e.g., demonstration of efficacy) or support an approval decision. However, final determinations are made after a complete review of a marketing application and are based on the entire data in the application.
SPA Requests for a Single Trial Intended to Support Marketing Approval
<i>Note: You may also apply these concepts to a trial for which you are not seeking SPA agreement.</i>
2) If the protocol for your SPA request is intended to be used as the sole registration trial to support marketing approval, this single trial should be optimally designed and the development program optimally planned. Therefore, you should address the following in your SPA request, and you may also briefly describe these items in your EOP2 meeting briefing document: <ul style="list-style-type: none"> • Justification of why a single trial and not multiple trials are appropriate or not possible for drug development and marketing approval for an NME or substantially different indication (e.g., a study is designed to show a clinically meaningful effect on mortality, irreversible morbidity, or prevention of disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. See 'Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products').

Type B

- A description of your drug development plan, including each indication that is being (or has been) studied and a timetable for submission of the planned studies. You should also include information on where the drug/biologic is marketed outside of the U.S. or indicate if an application for the drug/biologic has been submitted to foreign regulators.

Additional Content for SPA Request Submission

Note: You may also apply some of the concepts below to trials for which you are not seeking SPA agreement.

3) Please submit/address the items below in your SPA request.

- The protocol must be complete, including a FINAL detailed statistical analysis plan for the evaluation of primary and secondary clinical trial endpoints that potential claims will be sought. The cover letter should identify the need for an expert statistical review if the planned trial includes (1) adaptive design, (2) enrichment design, (3) non-inferiority hypotheses, or (4) novel, new or composite endpoints.
- If study is blinded, discuss toxicities of agents (or regimens) that may unmask blinding.
- If radiologic, you should discuss whether an external radiological review will be performed of primary endpoint
- If your trial uses an *in vitro* diagnostic test to identify the treatment population, you should meet with CDRH to discuss the plans for co-development of the diagnostic test prior to the SPA request. Also, you should provide your plans for a commercially available test at the time of proposed approval. The testing procedure used in your clinical trial should be identical (or "bridged") to your proposal for a commercial kit.
- If registration trial is to be primarily completed outside of the U.S., the following issues need to be addressed:
 - How assessment of safety and efficacy of U.S. minorities will be examined (e.g., will another study be conducted?)
 - Applicability of comparator treatment or of disease characteristics to U.S. population
- Any single arm submission should be accompanied by an adequate explanation of the reasons a randomized trial cannot be performed. Please refer to the transcripts for the February 8, 2011 ODAC on Accelerated Approval for Committee recommendations on single arm trials:
(www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM245644.pdf).

Accelerated or Regular Approval:

4) You should include a statement of whether you are seeking approval under 21 CFR 314 Subpart H/21 CFR 601 Subpart E (accelerated approval) or regular approval in your meeting briefing document, SPA request and NDA/BLA submission. If seeking accelerated approval, there should be a description of all protocols for confirmatory trials (including a timetable for expected trial initiation(s), completion of the planned trial(s), submission of final clinical study report(s)) in your SPA request and NDA/BLA submission. Under §314.510 and 601.41, confirmatory trials would usually be underway at the time of accelerated approval. Please refer to the transcripts for the February 8, 2011 ODAC on Accelerated Approval for Committee recommendations on the timing and number of confirmatory trials:
(www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM245644.pdf).

Type B

- If surrogate endpoint is being used for accelerated approval, you should justify (i.e., from the literature) why the proposed effect on this surrogate is reasonably likely to predict clinical benefit.

NDA/BLA content and format
CLINICAL
1) Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.
2) Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.
3) Investigator instructions that may have been produced in addition to the protocol and investigator brochure
4) All randomization lists and, if used, IVRS datasets (in SAS transport format)
5) All datasets used to track adjudications (in SAS transport format)
6) A Reviewers Guide to the data submission that includes, but is not limited to the following: <ol style="list-style-type: none"> a) description of files and documentation b) description of selected analysis datasets c) key variables of interest, including efficacy and safety variables d) SAS codes for sub-setting and combining datasets e) coding dictionary used f) methods of handling missing data g) list of variable contained in every dataset h) listing of raw data definitions i) analysis data definitions j) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item) k) documentation of programs
7) Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf).
8) Pediatric Studies: All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the FDA Pediatric Team at Pedsdrugs@fda.hhs.gov . You may also refer to the

Type B

following FDA website:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>

9) Quantitative Safety Analysis Plan (QSAP):

The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. When unanticipated safety issues are identified the QSAP may be amended. At a minimum the Safety Analysis Plan should address the following components:

- a) Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment, (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).
- b) Safety endpoints for Adverse Events of Special Interest (AERI)
- c) Definition of Treatment Emergent Adverse Event (TEAE)
- d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology Review Charter))
- e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
- f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.

10) Integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:

- a) Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf)
- b) Cancer Drug and Biological Products-Clinical Data in Marketing Applications (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf)

11) Perform the following Standard MedDRA Queries (SMQs) on the ISS adverse event data and include the results in your ISS report. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.

12) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application

13) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.

14) References:

Type B

There should be active links from lists of references to the referenced article.
Studies, Data And Analyses
15) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).
16) Provide a table with the following columns for each of the completed Phase 3 clinical trials: <ol style="list-style-type: none"> a) Site number b) Principle investigator c) Location: City State, Country d) Number of subjects screened e) Number of subjects randomized f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection) g) Number of protocol violations (Major, minor, including definition)
17) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).
18) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision. Narrative summaries should contain the following components: <ol style="list-style-type: none"> a) subject age and gender b) signs and symptoms related to the adverse event being discussed c) an assessment of the relationship of exposure duration to the development of the adverse event d) pertinent medical history e) concomitant medications with start dates relative to the adverse event f) pertinent physical exam findings g) pertinent test results (for example: lab data, ECG data, biopsy data) h) discussion of the diagnosis as supported by available clinical data i) a list of the differential diagnoses, for events without a definitive diagnosis j) treatment provided k) re-challenge and de-challenge results (if performed) l) outcomes and follow-up information m) an informed discussion of the case, allowing a better understanding of what the subject

Type B

experienced.
19) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request.
20) Provide reports for any autopsies conducted on study.
21) For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.
22) Regulations require that the safety and effectiveness data be presented for subgroups including “by gender, age, and racial subgroups”. Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis
23) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including: <ul style="list-style-type: none"> a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling. b) Exposure-Response Relationships – important exposure-response assessments. c) Less common adverse events (between 0.1% and 1%). d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values. e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers. f) Marked outliers and dropouts for laboratory abnormalities. g) Analysis of vital signs focused on measures of central tendencies. h) Analysis of vital signs focused on outliers or shifts from normal to abnormal. i) Marked outliers for vital signs and dropouts for vital sign abnormalities. j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value. k) Overview of ECG testing in the development program, including a brief review of the

Type B

<p>nonclinical results.</p> <p>l) Standard analyses and explorations of ECG data.</p> <p>m) Overdose experience.</p> <p>n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.</p> <p>o) Explorations for:</p> <p>i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.</p> <p>ii) Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.</p> <p>iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.</p> <p>iv) Drug-demographic interactions</p> <p>v) Drug-disease interactions</p> <p>p) Drug-drug interactions</p> <p>i) Dosing considerations for important drug-drug interactions.</p> <p>ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.</p>
<p>24) Marketing applications must include the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Provide all appropriate data as well as a clinical study report for any study performed to evaluate QT/QTc prolongation.</p>
<p>Financial Disclosure Information</p>
<p>25) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm).</p>

Physician's Labeling Rule

Highlights

- | |
|--|
| <p>1) Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]</p> |
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Type B

2) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3) The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4) The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5) The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to 21 CFR 201.57(a) (4) and to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom).
6) For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d) (9) and Implementation Guidance]. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).
7) 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: (a) "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."
8) Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
9) Refer to 21 CFR 201.57 (a) (11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
10) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a) (11)].
11) Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights
12) The Patient Counseling Information statement must appear in Highlights and must read "See 17 for PATIENT COUNSELING INFORMATION." [See 21 CFR 201.57(a)(14)]
13) A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a) (15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
14) A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Type B

Table of Contents
15) The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
16) The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
17) Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
18) Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
19) When a subsection is omitted, the numbering does not change [see 21 CFR 201.56(d) (1)]. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows: 8.1 Pregnancy 8.3 Nursing Mothers (<i>not 8.2</i>) 8.4 Pediatric Use (<i>not 8.3</i>) 8.5 Geriatric Use (<i>not 8.4</i>)
20) When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Full Prescribing Information (FPI)
22) Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23) Other than the required bolding [See 21 CFR 201.57(d) (1), (d) (5), and (d) (10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
24) Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format” (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf).
25) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf]

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26) Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27) Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
28) The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA-Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
29) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
30) The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
31) If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
32) Refer to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format.
33) Refer to the Institute of Safe Medication Practices’ website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

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/s/

SHARON K SICKAFUSE
03/24/2014