

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206995Orig1s000

OTHER REVIEW(S)

MEMORANDUM
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)

****Pre-decisional Agency Information****

Memorandum

Date: June 2, 2015

To: Sharon Sickafuse, RPM
Division of Oncology Products 2 (DOP2)
Office of Hematology Oncology Products (OHOP)

From: Marybeth Toscano, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP comments on draft product labeling for Iressa (gefitinib)
tablets
NDA 206995

In response to your consult request dated September 25, 2014, OPDP has reviewed the proposed product labeling (PI) for Iressa. OPDP's comments are based on the proposed draft of the PI, sent to OPDP on May 12, 2015. OPDP has reviewed the proposed PI, and our comments are highlighted in yellow in the attached draft.

If you have any questions, please contact Marybeth Toscano at 6-2617 or at Marybeth.Toscano@fda.hhs.gov.

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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/s/

MARYBETH TOSCANO
06/02/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 26, 2015

To: Patricia Keegan, MD
Director
Division of Oncology Products 2 (DOP2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Marybeth Toscano, Pharm D, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): IRESSA (gefitinib)

Dosage Form and Route: tablets for oral use

Application Type/Number: NDA 206995

Applicant: AstraZeneca Pharmaceuticals LP

1 INTRODUCTION

On September 17, 2014, AstraZeneca Pharmaceuticals LP submitted for the Agency's review a 505(b)(1) New Drug Application (NDA) 206995 for IRESSA (gefitinib) tablets. The purpose of this submission is to seek approval for the proposed indication 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) substitution mutations as detected by an FDA-approved test.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on September 25, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for IRESSA (gefitinib) tablets.

2 MATERIAL REVIEWED

- Draft IRESSA (gefitinib) Tablets PPI received on September 17, 2014, and received by DMPP and OPDP on September 25, 2014.
- Draft IRESSA (gefitinib) Tablets Prescribing Information (PI) received on September 17, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 12, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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/s/

BARBARA A FULLER
05/26/2015

LASHAWN M GRIFFITHS
05/26/2015

MARYBETH TOSCANO
05/27/2015

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: April 24, 2015

TO: Sharon Sickafuse, Regulatory Health Project Manager
Dickran Kazandjian, M.D., Medical Reviewer
Division of Oncology Products 2

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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THROUGH: Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
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Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206995

APPLICANT: AstraZeneca Pharmaceuticals LP

DRUG: IRESSA™ (gefitinib, ZD1839) Tablets

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard

INDICATION(S): For the 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.

CONSULTATION REQUEST DATE:	December 2, 2014
INSPECTION SUMMARY GOAL DATE:	May 1, 2015
DIVISION ACTION GOAL DATE:	July 17, 2015
PDUFA DATE:	July 17, 2015

I. BACKGROUND:

AstraZeneca Pharmaceuticals LP (AstraZeneca) seeks approval to market gefitinib for the 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. Gefitinib is an orally active, potent, reversible, and selective inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase (TK). This receptor exists as a monomer that dimerizes following binding of a ligand to the extracellular portion of the EGFR; this activates intrinsic protein TK activity resulting in tyrosine autophosphorylation. This leads to the initiation of numerous intracellular signal transduction pathways, which are implicated in the proliferation and survival of cancer cells and other host-dependent processes promoting cancer cell growth. Selective inhibition by gefitinib of EGFR TK interrupts the mitogenic and survival signals responsible for cellular cancer processes such as proliferation, growth, metastases, and angiogenesis.

IRESSA (gefitinib) 250 mg tablets (NDA 21-399) received accelerated approval on May 5, 2003 under 21 CFR 314, subpart H as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. Following the results of the 3 Phase III confirmatory studies IBREESE (D7913C00710), ISEL (D7913C00709), and INTEREST (D791GC0001), on June 28, 2005, the indication was restricted to use in only those patients already receiving and benefiting from IRESSA therapy. In September 2011, the NDA was voluntarily withdrawn, which was published in the Federal Register on April 25, 2012. Following the results of these studies, AstraZeneca continued to investigate the efficacy of gefitinib in the selected patient population with EGFR mutation-positive advanced or metastatic NSCLC.

The key study supporting this application is Study D791AC00014 (IFUM). This was an open-label, multicenter, single-arm study to characterize the efficacy, safety, and tolerability of gefitinib (250 mg orally once daily) as first-line treatment in Caucasian patients having locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring activating sensitizing epidermal growth factor receptor (EGFR) mutations. Patients with activating sensitizing EGFR tyrosine kinase (TK) mutations (EGFR M+) were eligible for this study. The study recruited Caucasian female or male patients aged ≥ 18 years with histologically confirmed, locally advanced or metastatic (Stage IIIA/B not suitable for therapy of curative intent or Stage IV) NSCLC eligible for standard first-line treatment. Caucasians were considered to be patients of European, North African, or Middle Eastern descent only for the purpose of this study. Patients of Indian, Pakistani, or Afghan origin were not eligible for this study.

Screening of approximately 1250 Caucasian NSCLC patients was expected to be sufficient to obtain 100 eligible (EGFR M+) patients for treatment with gefitinib. A total of 1060 Caucasian patients with locally advanced or metastatic NSCLC were screened, and 118 of these patients had an activating sensitizing EGFR mutation. A total of 106 of the 118 EGFR M+ patients received at least 1 dose of gefitinib.

A total of 75 centers from the following 13 countries participated in the study: Bulgaria (7 centers), France (2), Greece (6), Hungary (11), Italy (4), Norway (3), Poland (10), Portugal (4), Romania (7), Spain (5), Switzerland (4), Turkey (4), and the United Kingdom (UK) (8). The study was not conducted under IND.

The primary efficacy outcome measure was overall response rate (confirmed Complete Response or Partial Response) as determined by a blinded, central, independent review. For this study the central independent review function was contracted to a CRO, (b) (4). The purpose of the CRO inspection assignment memorandum was to assess data reliability generated by the CRO for Study D791AC00014 (IFUM).

II. RESULTS (by Site):

Name of CRO, Location	Protocol # Site #	Inspection Date	Final Classification
(b) (4)			

Rationale for Site Selection: Sites 6106, 7005 and 3303 were selected due to enrollment of large numbers of study subjects, and significant primary efficacy results pertinent to decision making. The remaining three sites were selected randomly by the FDA field investigator.

Key to Classifications

- NAI = No deviation from regulations.
- VAI = Deviation(s) from regulations.
- OAI = Significant deviations from regulations. Data unreliable.
- Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **CRO:** (b) (4) **(Blinded Independent Central Review (BICR) Vendor)**
- a. **What was inspected:** The CRO was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection focused primarily on assessing the integrity of the tumor response and disease progression source records for data generated by the Blinded Independent Central Review (BICR) Vendor, for the clinical study, D791AC00014 (IFUM), and comparing those source data to the data listings submitted to the application. The inspection also included a review of the firm's organization and personnel, staff and contract staff qualification and training, correspondence, quality assurance, data collection and handling, computer system validation, standard operating procedures review and adherence, and BICR Charter adherence.
- b. **General observations/commentary:** Records and procedures were adequate, and generally well organized. The primary efficacy endpoint support data, tumor response, generated by the BICR Contractor and submitted to NDA 206995 were verifiable for six clinical sites referred to in the table above. For all six sites, all subjects' image readings performed by the CRO radiologist were verified against the data listings submitted to the application; 36 subject endpoints and 239 subject timepoints. The CRO generated a total of 104 subject endpoints and 757 subject timepoints. Also, there was no evidence of BICR non-compliance with the Charter. No Form FDA 483 was issued.
- c. **Assessment of data integrity:** The data from this contractor, (b) (4) (b) (4) who performed the function of the Blinded Independent Central Review (BICR)/Central Imaging Vendor, associated with Study D791AC00014 (IFUM) in support of NDA 206995, appear reliable and may be used in support of the respective indication.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings, the data from Study D791AC00014 (IFUM) generated by CRO (b) (4), who performed the function of the Blinded Independent Central Review (BICR) Vendor, submitted to the Agency in support of NDA 206995, appear reliable.

The preliminary classification for the CRO Central Imaging Vendor (b) (4) is No Action Indicated (NAI).

Note: The observations noted above are based on the preliminary communications provided by the FDA field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIR.

{ See appended electronic signature page }

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/s/

LAUREN C IACONO-CONNORS
04/24/2015

SUSAN D THOMPSON
04/24/2015

KASSA AYALEW
04/24/2015

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	206995
Brand Name	Iressa
Generic Name	Gefitinib (ZD1839)
Sponsor	AstraZeneca UK LTD
Indication	First-line treatment of patients with (b) (4) metastatic non-small lung cancer (NSCLC) whose tumors have EGFR exon 19 deletion or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.
Dosage Form	Tablet
Drug Class	Epidermal growth factor receptor inhibitor
Therapeutic Dosing Regimen	250 mg
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	In patients: Gefitinib 525 mg oral daily (Studies D7913C00005, V-15-11) Gefitinib 600 mg oral daily (Studies D7913C00011 and D7913C00012) Gefitinib 3500 mg oral weekly or 2000 mg oral twice weekly (Study D7913C00022)
Submission Number and Date	SDN001/ 9-17-2014
Review Division	DOP2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

In this submission, ECG assessment for gefitinib was performed based on data from a Phase II efficacy trial (Study D4200C00003). The study was conducted in 2 parts. In Part A patients were randomized to one of the two double-blind treatment arms (gefitinib or vandetanib (also called ZD6474)). In Part B patients received the alternative study treatment to that given in Part A. Based on data from Part A at the steady state, no large change (i.e., > 20 ms) in the QTcF interval was detected when single daily multiple doses of 250 mg gefitinib was administrated. The sponsor did not obtain placebo and positive control (moxifloxacin) arms. Therefore, no assay sensitivity was established.

In this study, approximately 160 patients received a repeated single daily dose of 250 mg gefitinib from Part A. Overall summary findings from Part A are presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds of Δ QTcF for Gefitinib 250 mg (FDA Analysis Based on Part A Steady State Day by Pooling Study Days 8, 15, 22, 29 and 57)

Treatment	Time (hour)	Mean	Std Dev	90% CI (ms)
Gefitinib 250 mg	7	-6.5	15.0	(-20.8, 7.8)

The applicant submits data following the approved dosing regimen of 250 mg. The exposure range is expected to cover the therapeutic exposures in the typical patients population. However, the exposure following 250 mg administration is not expected to reach the exposure when gefitinib is administered with CYP3A4 inhibitor ketoconazole.

2 PROPOSED LABEL

The sponsor proposed the following QT-related labeling change:

Data from non-clinical (*in vitro and in vivo*) studies indicate that gefitinib has the potential to inhibit cardiac action potential repolarization process (e.g. QT interval).

(b) (4)

We agree with the sponsor that no significant QT prolongation has emerged in this study. We defer final labeling decisions to the Division.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Gefitinib (ZD1839, IRESSA™) is a potent and selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase.

3.2 MARKET APPROVAL STATUS

IRESSA was first approved for marketing in Japan in 2002 and then in US in 2003. It is currently approved in 90 countries for patients with locally advanced or metastatic Non-Small Cell Lung Cancer (aNSCLC) who have activating mutations of the EGFR tyrosine kinase.

3.3 PRECLINICAL INFORMATION

From the Iressa label:

Data from non-clinical (*in vitro and in vivo*) studies indicate that gefitinib has the potential to inhibit the cardiac action potential repolarization process (eg, QT interval).

(b) (4)

3.4 PREVIOUS CLINICAL EXPERIENCE

A comprehensive pre- and post-launch development program consisting of over 60 AstraZeneca sponsored clinical studies has contributed to the safety data available for gefitinib. According to the sponsor, an Independent Expert Cardiologist Review was conducted to assess the collected ECGs from Phase I and II studies which included more detailed ECG methodology. This review concluded that there was no QT liability for gefitinib in the dose range of 225 mg to 1000 mg once daily. Additionally, a thorough review of AE data from 30 clinical pharmacology studies was conducted to identify any cardiac safety events per ICH E14 guidelines, including any that could potentially link to QT interval prolongation or clinical pro-arrhythmic events. There was no signal indicating a possible effect of gefitinib treatment on QT prolongation in early clinical studies that warranted further rigorous ECG monitoring in Phase III studies. Therefore in

subsequent AstraZeneca sponsored randomized phase III studies intensive ECG monitoring was not applied.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of gefitinib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The applicant has submitted data from Study D4200C00003 as well as a population PKPD report. Study D4200C00003 is not a TQT study.

4.2 TQT STUDY

The applicant used ECG data from a Phase II (Study ID: D4200C00003) study to investigate the QT prolongation potential of gefitinib.

4.2.1 Title

A Phase II, Randomized, Double-blind, 2-Part, Multicenter Study To Compare the Efficacy of ZD6474 with the Efficacy of ZD1839 (Iressa™) in Patients With Locally Advanced or Metastatic (IIIB/IV) Non-small Cell Lung Cancer after Failure of either First-Line and/or Second-line Platinum-based Chemotherapy and to Assess the Activity of ZD6474 in Patients Following Failure of Treatment With ZD1839

4.2.2 Protocol Number

D4200C00003

4.2.3 Study Dates

First patient enrolled: 22 May 2003

Last patient enrolled: 16 August 2004

4.2.4 Objectives

- To derive parameters that describe the pharmacokinetics of once daily multiple doses of 250 mg gefitinib and assess inter-individual and residual variability in this patient population
- To investigate potential associations between exposure to gefitinib and QT measurements (Bazett's and Fridericia's correction formulae, QTcB and QTcF respectively)

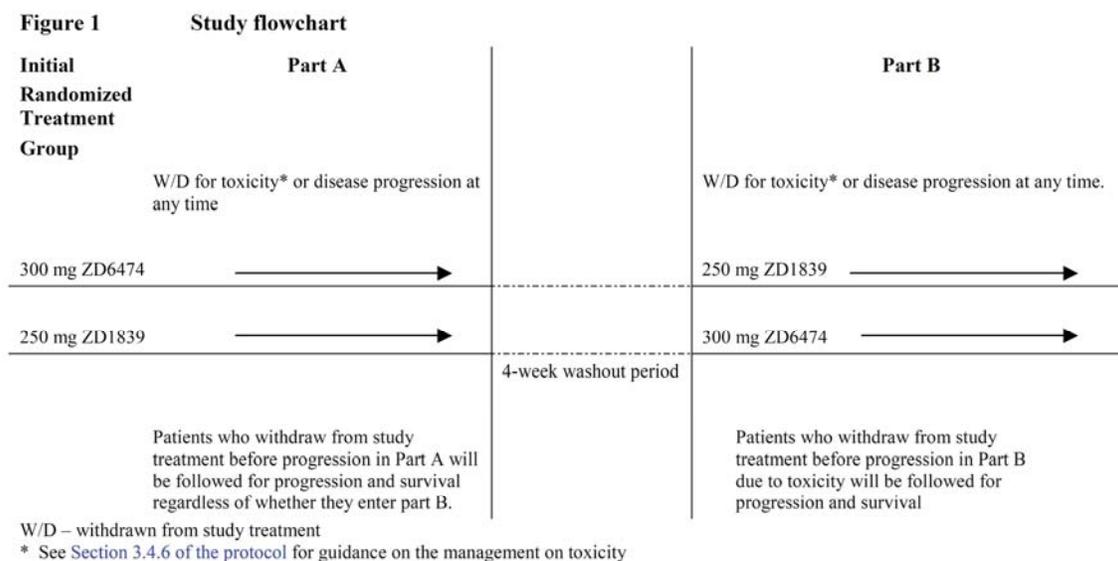
Comparing the efficacy of ZD6474 with the efficacy of gefitinib (Iressa™) in subjects with locally advanced or metastatic (IIIB/IV) non-small cell lung cancer (NSCLC) after failure of either first-line and/or second-line platinum-based chemotherapy.

4.2.5 Study Description

4.2.5.1 Design

The study was conducted in 2 parts. In Part A patients (approximately 160) were randomized to one of two double-blind treatment arms (ZD6474 or gefitinib). In Part B patients received the alternate study treatment to that given in Part A. To maintain the study blind, blood samples were taken from all patients in both treatment arms for determination of ZD6474 and gefitinib plasma concentrations using a dual assay (ZD6474 and gefitinib were quantified from the same sample). Only the gefitinib data from Part A of this study was used in this analysis. The rationale for this is that ZD6474 has a very long half-life and treatment could not be withheld from patients therefore only a short washout period prior to the start of Part B was possible. This resulted in significant residual concentrations of ZD6474 in the patients taking gefitinib in Part B. Since ZD6474 is known to modulate QT, this would confound any analysis of a gefitinib effect.

Figure 1. Study Flow Chart.



Note: Only part one data from 250 mg gefitinib (ZD1839) are used for this analysis
Source: Figure 1, \\cdsesub1\evsprod\nda206995\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\d4200c00003\d4200c00003-legacy-csr.pdf

4.2.5.2 Controls

There was no placebo or positive control for QT in this trial.

4.2.5.3 Blinding

The trial was double blind for gefitinib or vandetanib (ZD6474).

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Only Part A data from once daily 250 mg gefitinib (ZD1839) are used for this analysis.

4.2.6.2 Sponsor's Justification for Doses

The applicant does not provide a dose justification in their report.

Reviewer's Comment: The 250-mg dose is the approved dose. Exposures following a supratherapeutic dose are not available.

4.2.6.3 Instructions with Regard to Meals

Subjects were instructed to fast 2 hours before and after dosing.

Reviewer's Comment: Gefitinib label states that bioavailability is not significantly affected by food. Furthermore, the label states that gefitinib should be administered without food. Applicant's recommendations are therefore appropriate.

4.2.6.4 ECG and PK Assessments

PK assessment:

- Pre-dose and 1, 3, 5,7 and 24 hours post dose on the first day of dosing (study day 1) from a minimum of 60 patients.
- Pre-dose and 1, 3, 5,7 and 24 hours post dose on study day 29.
- Weekly, within a window of 4 to 8 hours post dose, for the first 8 weeks of dosing.
- A pre-dose sample and a sample taken within a 4 to 8 hour post dose window, were taken on study day 57. A further post dose sample was taken within this window in the following 4 weeks.
- Extra sampling was undertaken in the event of a QT prolongation.

ECG assessment:

...screening and between 4 and 8 hrs post dose on study days 1, 8, 15, 22 and 29. On study days 29 and 57 an additional pre-dose ECGs will be obtained. If no QT prolongation was present, ECGs were performed weekly for the first 2 cycles and every 4 weeks for all subsequent cycles. Further ECG assessments were undertaken in the event of a QT prolongation. It was planned that PK samples were taken within 15 minutes of the ECG assessment or as soon as possible.

Reviewer's Comment: According to gefitinib's label, C_{max} occurs 3 to 7 hours after dosing. However, in this study ECG and PK sampling time points were not matched.

4.2.6.5 Baseline

The sponsor used the average of the screening and Day 1 pre-dose QT values as baselines.

4.2.7 ECG Collection

In this study, 12-lead digital ECGs were performed.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Form Part A, approximately 160 subjects were randomized to one of two double-blind treatment arms (ZD6474 or gefitinib).

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The sponsor did not perform E14 analysis.

Reviewer's Comments: We will provide our independent analysis result in Section 5.2. Statistical reviewer performed summary statistics and analyses of $\Delta QTcF$ for days 1, 8, 15, 22, 29 and 57 and pooled those study days.

4.2.8.2.2 Assay Sensitivity

There is no assay sensitivity established in this study because no positive control arm was included.

4.2.8.3 Safety Analysis

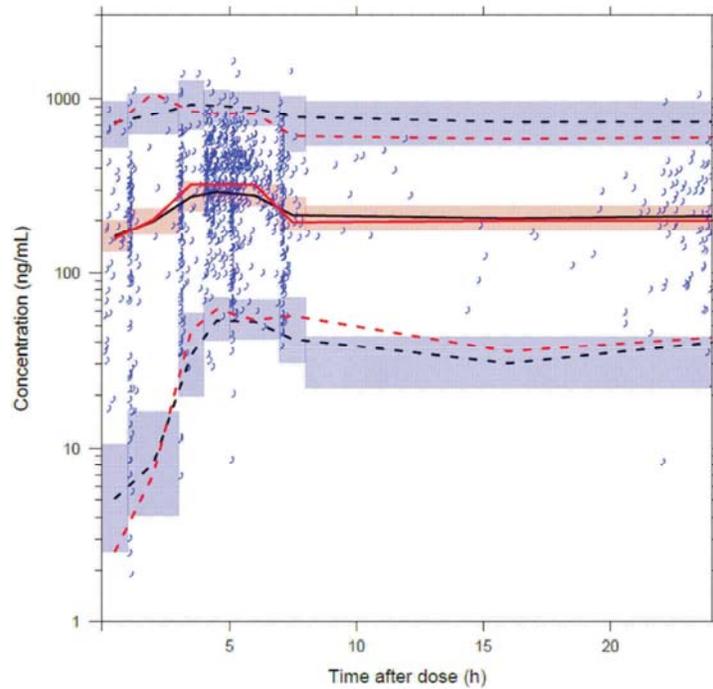
The sponsor did not conduct a safety analysis.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The applicant has submitted a population PK/PD model. The PK of gefitinib 250 mg, the approved dose, was characterized in Figure 2.

Figure 2: Gefitinib Concentration-Time Course



Source: Figure 9 in the applicant's population PK report. Red lines indicate observed median, 2.5, and 97.5 percentiles. Black lines indicate the corresponding model predictions. The shaded areas represent the confidence interval of the model predictions.

4.2.8.4.2 Exposure-Response Analysis

The applicant analyzed the relationship between plasma concentration and QTcB or QTcF using nonlinear mixed effect modeling in NONMEM. The relationship between individual predicted (IPRED) concentrations and QTcF or QTcB was estimated with a linear mixed effect model, with no apparent relationship.

Figure 3: Individual Predicted Plasma Concentration vs. Observed QTcF or QTcB. Predictions Are Shown in Red.

Figure 10 Final PKPD QTcB model: observed and fitted QTcB measurements versus individual predicted concentration

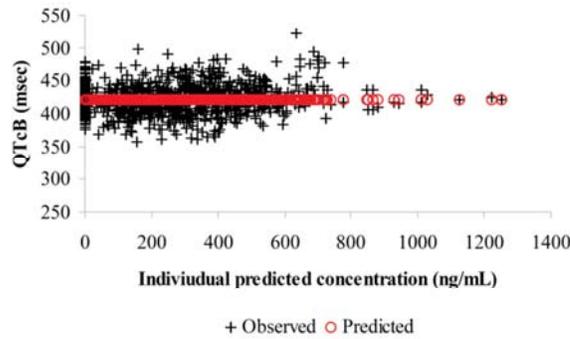
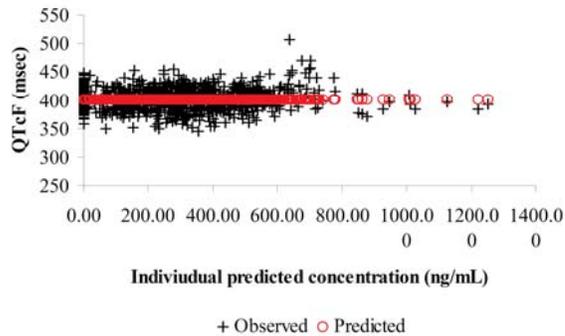


Figure 11 Final PKPD QTcF model: observed and fitted QTcF measurements versus individual predicted concentration



Source: Figures 10 and 11 in the applicant's report.

Reviewer's comment: The population PKPD report has not been subject to a formal pharmacometric review. ECG and PK sampling time were not matched in this trial. The sponsor therefore used individual predicted concentrations to estimate the exposure-response relationship for QT assessment. The applicant's assumption about time delay between effect and concentrations is not supported by the data. This reviewer does not think that the current PKPD exploratory practice is able to rule out a concentration-QT relationship for gefitinib.

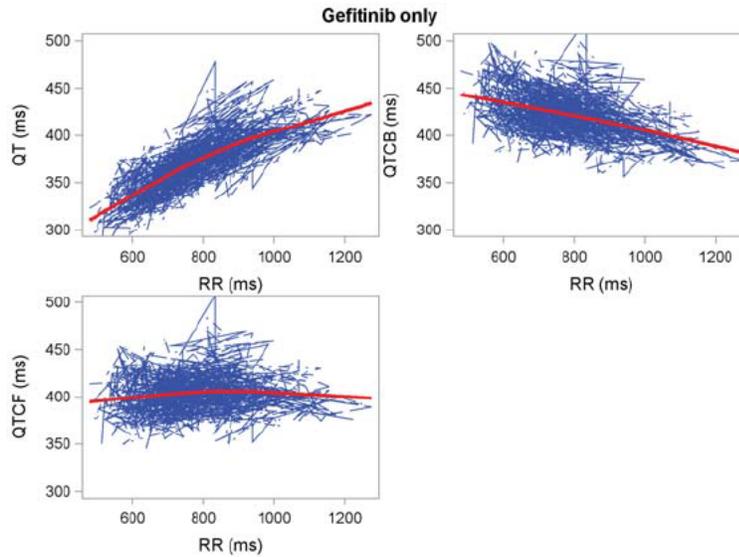
5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

This review did not evaluate of the QT/RR correction method because the sponsor only provided QTcB and QTcF correction intervals. This reviewer chose to present QTcF for the primary statistical analysis.

The relationship between different correction methods and RR is presented in Figure 4.

Figure 4: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



Note: Only Part A data from 250 mg gefitinib (ZD1839) are used. Study Days are Day 1, 8, 15, 22, 29 and 57.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Gefitinib 250 mg

The primary endpoint is change from baseline of QTcF. The descriptive statistics are listed in Table 2 to Table 8. The sponsor ECG assessment based on screening and between 4 and 8 hours post dose on study days 1, 8, 15, 22, 29 and 57. Based on data from Part A at the steady state, no large change (i.e., > 20 ms) in the QTc interval was detected when administered gefitinib 250 mg. However, the largest upper bound of the 2-sided 90% CI for the mean difference is 38.6 ms, which is greater than 20 ms at Day 29.

Table 2: Analysis Results of Δ QTcF of Gefitinib 250 mg Part=A and Day=1

Time	N	Mean	Std Dev	90% CI for Mean
0.1	11	-7.6	17.0	(-16.9, 1.7)
5	32	-0.5	13.6	(-4.5, 3.6)
7	6	-3.0	14.4	(-14.9, 8.8)
8	37	1.1	14.7	(-2.9, 5.2)

**Table 3: Analysis Results of Δ QTcF of Gefitinib 250 mg
Part=A and Day=8**

Time	N	Mean	Std Dev	90% CI for Mean
0.1	11	-7.6	17.0	(-16.9, 1.7)

**Table 4: Analysis Results of Δ QTcF of Gefitinib 250 mg
Part=A and Day=15**

Time	N	Mean	Std Dev	90% CI for Mean
0.1	54	0.7	16.4	(-3.1, 4.4)

**Table 5: Analysis Results of Δ QTcF of Gefitinib 250 mg
Part=A and Day=22**

Time	N	Mean	Std Dev	90% CI for Mean
0.1	56	-0.1	14.5	(-3.3, 3.2)

**Table 6: Analysis Results of Δ QTcF of Gefitinib 250 mg
Part=A and Day=29**

Time	N	Mean	Std Dev	90% CI for Mean
0	41	-1.6	16.1	(-5.8, 2.7)
5	34	2.0	15.7	(-2.6, 6.5)
7	5	-6.5	15.0	(-20.8, 7.8)
8	2	3.7	7.8	(-31.2, 38.6)

**Table 7: Analysis Results of Δ QTcF of Gefitinib 250 mg
Part =A and Day=57**

Time	N	Mean	Std Dev	90% CI for Mean
0	22	-1.9	15.0	(-7.4, 3.6)
0.1	24	-4.0	14.0	(-8.9, 0.8)
8	5	-15.3	16.3	(-30.8, 0.3)

**Table 8: Analysis Results of Δ QTcF of Gefitinib 250 mg
(from Part=A at the Steady State)**

Time	N	Mean	Std Dev	90% CI for Mean
0	63	-1.7	15.6	(-5.0, 1.6)
5	34	2.0	15.7	(-2.6, 6.5)
7	5	-6.5	15.0	(-20.8, 7.8)
8	7	-9.8	16.5	(-22.0, 2.3)

5.2.1.1 Assay Sensitivity Analysis

No assay sensitivity established because no positive control arm was included in the study.

5.2.1.2 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcF values are \leq 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 9: Categorical Analysis for QTcF

TREAT	QTcF		
	450 ms<Value<=480 ms	Value<=450 ms	Total
ZD1839 250 mg/day	1	84	85

Table 10 lists the categorical analysis results for Δ QTcF. No subject's change from baseline was above 60 ms.

Table 10: Categorical Analysis of Δ QTcF

TREAT	QTcF_CFB		
	30 ms<Value<=60 ms	Value<=30 ms	Total
ZD1839 250 mg/day	4	61	65
Total	4	61	65
Frequency Missing = 20			

5.2.2 HR Analysis

The primary endpoint is the change from baseline of HR. The descriptive statistics are listed in Table 11. Based on data from Part A at the steady state, the largest upper bounds of the 2-sided 90% CI for the mean difference is 19.8 bpm. Table 12 presents the

categorical analysis of HR. Six subjects who experienced HR interval greater than 100 bpm are in gefitinib 250-mg group.

Table 11: Analysis Results of Δ HR of Gefitinib 250 mg (from Part=A at the Steady State)

Time	N	Mean	Std Dev	90% CI for Mean
0	63	-2.7	10.7	(-4.9, -0.4)
5	34	0.7	9.7	(-2.2, 3.5)
7	5	5.4	15.1	(-9.0, 19.8)
8	7	-3.8	14.0	(-14.0, 6.5)

Table 12: Categorical Analysis of HR

TREAT	HR		
	HR <= 100 bpm	HR >100 bpm	Total
ZD1839 250 mg/day	79	6	85

5.2.3 PR Analysis

The primary endpoint is the change from baseline of PR. The descriptive statistics are listed in Table 13. Based on data from Part A at the steady state, the largest upper bounds of the 2-sided 90% CI for the mean difference is 10.1 ms. Table 14 presents the categorical analysis of PR. Six subjects who experienced PR interval greater than 200 ms are in gefitinib 250-mg group.

Table 13: Analysis Results of Δ PR of Gefitinib 250 mg (from Part=A at the Steady State)

Time	N	Mean	Std Dev	90% CI for Mean
0	63	1.2	12.6	(-1.5, 3.9)
5	34	1.5	11.1	(-1.8, 4.7)
7	5	2.7	5.0	(-2.1, 7.5)
8	7	2.4	10.5	(-5.4, 10.1)

Table 14: Categorical Analysis for PR

TREAT	PR		
	PR <= 200 ms	PR >200 ms	Total
ZD1839 250 mg/day	79	6	85

5.2.4 QRS Analysis

The primary endpoint is the change from baseline of QRS. The descriptive statistics are listed in Table 15. Based on data from Part A at the steady state, the largest upper bounds of the 2-sided 90% CI for the mean difference is 2.2 ms. Table 16 presents the categorical analysis of QRS. Eleven subjects who experienced QRS interval greater than 110 ms are in gefitinib 250-mg group.

Table 15: Analysis Results of Δ QRS for Gefitinib 250 mg (from Part=A at the Steady State)

Time	N	Mean	Std Dev	90% CI for Mean
0	63	-0.5	8.3	(-2.3, 1.2)
5	34	0.1	7.2	(-1.9, 2.2)
7	5	-3.6	6.1	(-9.4, 2.2)
8	7	-3.5	6.2	(-8.1, 1.0)

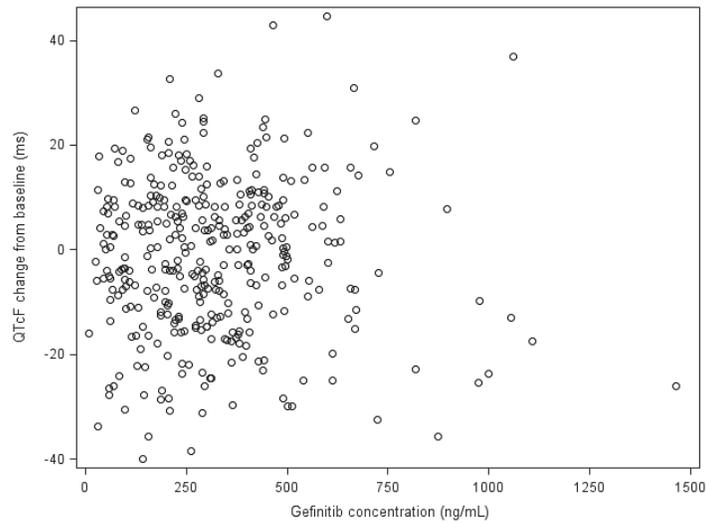
Table 16: Categorical Analysis for QRS

TREAT	QRS		Total
	QRS <= 110 ms	QRS > 110 ms	
ZD1839 250 mg/day	74	11	85

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The drug concentration-time profile is illustrated in Figure 2. The relationship between Δ QTcF and gefitinib concentrations is visualized in Figure 5 and with no evident exposure-response relationship. However, because ECG and PK sampling were not matched in this trial, the exploratory exposure-response analysis is not able to rule out a small concentration-QTc relationship for gefitinib.

Figure 5: Δ QTcF vs. Gefitinib Concentrations



Note: Only Part A data from 250 mg gefitinib (ZD1839) are used. Study Days are Day 1, 8, 15, 22, 29 and 57. Data with ECG/PK sampling time more than 30 minutes apart were excluded.

5.4 CLINICAL ASSESSMENTS

5.4.1 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.2 PR and QRS Interval

There was no clinically relevant effect seen on PR or QRS.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	Gefitinib 250 mg per day
Maximum tolerated dose	In patients: Gefitinib 525 mg oral daily (Studies D7913C00005, V-15-11) Gefitinib 600 mg oral daily (Studies D7913C00011 and D7913C00012 [with very limited PK information]) Gefitinib 3500 mg oral weekly or 2000 mg oral twice weekly (Study D7913C00022)
Principal adverse events	<p>The 30 clinical pharmacology studies included in NDA 206-995 involved healthy volunteers as well as patients. One of these studies (V-15-33) was a case-control study involving 1886 patients treated with gefitinib, which collected SAEs only. The most frequent SAEs within this study with a data cut off of $\geq 0.2\%$ included interstitial lung disease, pneumonia, lung disorder, cerebral infarction, pneumocystis jiroveci pneumonia, pneumonia bacterial, anorexia, vomiting, hepatic function abnormal and pyrexia. No dose limiting toxicity information was reported within this study.</p> <p>For the remaining 29 studies a more detailed review is presented in Appendix 2 where a data cut off of $\geq 10\%$ has been used to obtain the most frequent AEs and presented by individual studies. Within the Highlights Table, a data cut off of $\geq 20\%$ has been used for the 29 clinical pharmacology studies in order to present the overall most frequent AEs. These AEs are; headache, abdominal pain, asthenia/ fatigue, somnolence, cough, cough increased, diarrhoea, nausea, rash, acne, dyspnoea, vomiting, constipation, anorexia, pain, flu syndrome, conjunctivitis, corneal opacity, eye disorder, dry skin, pharyngitis, ALT/SGPT increased, injection site inflammation, injection site reaction, taste perversion, fever, leukocytosis, leukopenia, alkaline phosphatase increased, lactic dehydrogenase increased, AST/SGOT increased, weight loss, seborrhoea, haemorrhoids, stomatitis, peripheral oedema, sepsis, dyspepsia and eye pain.</p> <p>Of these most frequent AEs the following were reported to be experienced at a CTCAE grade 3 or higher; headache, dyspnoea, asthenia/fatigue, diarrhoea, rash, anorexia, cough, constipation, vomiting, weight loss, acne, nausea, cough increased, pain, pharyngitis, peripheral oedema, leukopenia, alkaline phosphatase increased, AST/SGOT increased and ALT/SGPT increased.</p> <p>Across the studies, the most common DLT was diarrhoea. Overall the following AEs were identified as drug-related DLT within the studies; diarrhoea, dehydration, ALT increased, AST increased, acne, vomiting and abdominal pain, gamma-glutamyl transpeptidase increased, pruritus, rash, dry skin, urticaria, ovarian pain, depression, somnolence, asthenia, hematemesis and hypokalemia.</p>

Maximum dose tested	Single Dose	IV dose: Gefitinib 100 mg in healthy volunteers (Study D7913C00031) Gefitinib 50 mg in patients (Study D7913C00035)
		Oral dose: Gefitinib 500 mg in healthy volunteers (Studies D7913C00030, D7913C00033, D7913C00051) Gefitinib 250 mg in patients (D7913C00035)
	Multiple Dose	Oral dose in healthy volunteers: Gefitinib 100 mg per day (Study D7913C00034) Oral dose in patients: Gefitinib 700 mg per day (Studies D7913C00005, V-15-11) Gefitinib 1000 mg per day (Studies D7913C00011, D7913C00012, [with very limited PK information]) Gefitinib 3500 mg weekly and 2000 mg twice weekly (Study D7913C00022)
Exposures achieved at maximum tested dose	Single Dose Multiple Dose	The maximum exposure achieved following a single dose or multiple doses is summarised in Table 2 .
Range of linear PK	<p>Across the range of dose levels studied in healthy volunteers (50 mg to 500 mg) and in cancer patients (50 mg to 700 mg), single-dose C_{max} and exposure ($AUC_{(0,24)}$ or AUC) appeared to increase in a dose-related manner.</p> <p>The dose proportionality was summarised in the NDA Module 2.7.2, Section 3.3.5.</p> <p>A formal assessment of the dose proportionality of single oral doses of 50, 100, 250 and 500 mg gefitinib in healthy volunteers was conducted in Study D7913C00033. Dose proportionality data were also obtained at steady state at the 250 mg and 500 mg doses used in the Phase II IDEAL studies (Studies D7913C00016 and D7913C00039).</p> <p>Assessment of dose proportionality was the primary objective of Study D7913C00033, in which dose proportionality in terms of AUC and C_{max} was evaluated using a statistical power model from which the proportionality coefficient (b) was estimated. Dose proportionality was to be concluded if the 90% CI for b fell within the limits 0.699 to 1.301 (limits which corresponded to a change in exposure that was between half and double the change in dose).</p> <p>Although within healthy volunteers both C_{max} and AUC increased with increasing dose, it was not possible to conclude proportionality for gefitinib over the dose range from 50 mg to 500 mg since for both parameters the upper 90% confidence limit for b was above the upper pre-determined limit. However, the departure from proportionality was small and it was estimated that if the administered dose were to be doubled, AUC and C_{max} values would increase by only 18% more than would be required to achieve proportionality.</p> <p>In a subsequent analysis of the data, pair-wise comparisons of the effect of dose on dose-normalised endpoints revealed that AUC/dose was significantly greater for the 500 mg dose than for the 50, 100 or 250 mg doses, and that C_{max}/dose was significantly greater for the 500 mg dose than for the 50 mg and 250 mg doses. These results suggested that the main influence on the non-proportionality of gefitinib over this range was at the 500 mg dose level. Consequently, up to the gefitinib dose proposed for therapeutic use in NSCLC (250 mg), dose proportionality following single dosing appeared to hold in healthy volunteers.</p> <p>Based on data obtained from cancer patients in the Phase I studies, there is no reason to believe that dose proportionality will not also hold across this range in cancer patients. At steady state in cancer patients dose proportionality was suggested, at least in the trough concentrations, at gefitinib doses of 250 mg and 500 mg.</p> <p>In conclusion, although there is some evidence of a small non-proportionality in exposure following single doses in healthy volunteers this does not appear to have been observed in the most relevant setting in cancer patients. In addition, since only 1 fixed dose of gefitinib is being proposed for therapeutic use it is unlikely that any issues related to non-proportionality would occur.</p>	

Distribution	Vd/F or Vd	<p>Study D7913C00031 (100 mg IV in healthy volunteers): mean: 1530 L (SD: 146 L)</p> <p>Study D7913C00035 (50 mg IV in patients): mean: 1400 L (SD: 504 L)</p>
	Percentage bound	Mean: 91 (CV [percentage]: 0.8)
Elimination	Route	Study D7913C00003: 86% of total radioactivity recovered from faeces, <4% in urine
	Terminal t _{1/2}	<p>Parent</p> <p>Study D7913C00031:</p> <p>Gefitinib 50 mg IV in healthy volunteers: mean 40.3 hours (SD: 22.1)</p> <p>Gefitinib 100 mg IV in healthy volunteers: mean 27.9 hours (SD: 2.4)</p> <p>Study D7913C00035:</p> <p>Gefitinib 50 mg IV in patients: mean 48.3 hours (SD: 27.3)</p> <p>Mean (CV [percentage]) for metabolites: Not calculated</p>
Elimination (continued)	CL/F or CL ml/min	<p>Study D7913C00031:</p> <p>Gefitinib 50 mg IV in healthy volunteers: mean 692.7 (CV [percentage]: 27.74)</p> <p>Gefitinib 100 mg IV in healthy volunteers: mean 1016 (CV [percentage]: 21.40)</p> <p>Study D7913C00035:</p> <p>Gefitinib 50 mg IV in patients: mean 513.64 (CV [percentage]: 59.26)</p>
Intrinsic factors	Age	A specific study in elderly healthy volunteers has not been conducted. From the results of the population PK analysis, no clear relationship was seen between the individual predicted trough concentration of gefitinib and the patient's age.
	Sex	A difference in exposure by gender was not identified in cancer patients with the exception of 1 study where population PK analysis showed that females had higher exposure than males.
	Race	<p>In a Phase I study (Study V-15-11) conducted in Japan, gefitinib was administered orally to male and female patients with advanced solid tumours at doses of 50, 100, 225, 400, 525 and 700 mg. PK data generated in this study were compared with those generated in Study D7913C00005 to identify any inter-ethnic differences in the PK of gefitinib.</p> <p>Visual comparison of the overall shape of the plasma concentration-time profiles obtained from the patients in Study V-15-11 following single and multiple-dosing, compared with those obtained in Western patients in Study D7913C00005, suggests that there was similarity in the PK of orally-administered gefitinib between Japanese and non-Japanese patients. Furthermore, comparison of individual values for the derived PK parameters in the 2 studies suggests that although at each dose level there was a range of up to 8-fold in inter-patient values, the values were similar between Japanese and non-Japanese patients.</p>

	Hepatic and renal impairment	<p>Study D7913C00032 was conducted in patients with advanced solid tumours, and either normal hepatic function or moderate hepatic impairment due to metastases. At steady state the ratio of glsmeans for patients with moderate hepatic impairment: normal hepatic function was:</p> <p>AUC_{ss}: 1.07</p> <p>C_{ss,max}: 1.11</p> <p>A renal impairment study has not been conducted.</p>
Extrinsic factors	Drug interactions	<p>Study D7913C00051: Effect of itraconazole on the PK of gefitinib</p> <p>At gefitinib 250 mg (ratio of with and without itraconazole)</p> <p>C_{max}: 1.51</p> <p>AUC: 1.78</p> <p>Study D7913C00030 Effect of rifampicin on the PK of gefitinib</p> <p>At gefitinib 500 mg (ratio of with and without rifampicin)</p> <p>C_{max}: 0.351</p> <p>AUC: 0.167</p>
	Food effects	<p>Study D7913C00036: at a gefitinib 250 mg dose, glsmean of C_{max} and AUC were increased by 32% and 37%, respectively, in the presence of high fat food.</p>
	Elevated gastrointestinal pH	<p>Study D7913C00036</p> <p>Sustained elevation of gastric pH (above 5 for an 8 hour period) resulted in a reduction in exposure to gefitinib (71% reduction in glsmean C_{max}; 47% reduction in glsmean AUC). In most healthy volunteers (60%), gefitinib absorption was reduced, with lower plasma concentrations observed over the whole plasma concentration-time profile. In the remaining healthy volunteers, a similar reduction in plasma concentrations was seen over the first 24 hours post-dose, but the profiles thereafter were indicative of prolonged absorption, suggesting that in these individuals there was continued absorption of gefitinib as the drug passed down the gastrointestinal tract.</p>
Expected high clinical exposure scenario	<p>The worst case scenario was observed from the following 2 drug-drug interaction studies:</p> <p>Study D7913C00051: Effect of itraconazole on the PK of gefitinib</p> <p>At gefitinib 250 mg (ratio of with and without itraconazole)</p> <p>C_{max}: 1.51</p> <p>AUC: 1.78</p> <p>Study D7913C00030 Effect of rifampicin on the PK of gefitinib</p> <p>At gefitinib 500 mg (ratio of with and without rifampicin)</p> <p>C_{max}: 0.351</p> <p>AUC: 0.167</p>	
Preclinical cardiac safety	<ul style="list-style-type: none"> • Nonclinical data from specific studies evaluating the potential for gefitinib to affect QT interval are summarised in Module 2.6.2.4. • In the hERG assay, gefitinib had an IC₅₀ of 1 µM. • In dog isolated Purkinje fibres there was prolongation of APD₉₀ at concentrations of 3 µM and 10 µM (Studies TSD1212 and TSD1292). • Effects in vitro occur at drug concentrations above a reference value for the mean human C_{max, free} level following a 250 mg dose. • No statistically significant increase in QTc was noted in telemetered dogs following single doses of 5 mg/kg or 50 mg/kg (where peak plasma levels would be greater than 20 x above the human mean C_{max, free} at 250 mg). <p>Further information is provided in Section 3.</p>	

Clinical Cardiac Safety The total number of clinical pharmacology studies is summarized in [Appendix 1](#). The total number of subjects at each drug exposure level is not summarized considering the high intra-subject variation in gefitinib exposure (up to 2 fold for AUC and up to 3 fold for C_{max} , NDA 2.7.2, Section 3.2.4.3). Thus, the total number of subjects at each dose level is provided below. In addition, a population PK analysis to explore the exposure and ECG measurement was provided (Section 4.3.2) which showed there is no relationship between gefitinib exposure and QT interval.

The dose of gefitinib administered in the 30 Clinical Pharmacology studies varied and is summarised in the following table:

Dosage of gefitinib (mg/day)	Number of Subjects Exposed
<250	170
250	2534
300 - 400	73
500	256
>500	111

In addition, 15 subjects received multiple ascending doses of gefitinib at doses of either 50, 100 and 500 mg or 50, 250 and 500 mg. A further 19 subjects received a single IV dose of 50 mg gefitinib followed by a 3 week washout and a single oral dose of 250mg. Additional information on the dosing regimens used in the Clinical Pharmacology studies can be found in [Appendix 1](#) the Tabular List of Studies.

Cardiac safety related events per ICH E14 guidelines from the clinical pharmacology studies are presented in Section 4.4. There were 44 events reported from 33 subjects in the 30 clinical pharmacology studies.

AE Adverse event; ALT Alanine transaminase; APD₉₀ Action potential duration at 90% of repolarisation; AUC Area under the concentration versus time curve; AUC_(0,24) Area under the concentration versus time curve at 0 to 24 hours; AUC_{ss} Area under the concentration versus time curve at steady state; CI Confidence interval; CL Clearance; CL/F Apparent clearance; C_{max} Maximum plasma concentration; $C_{max,free}$ Fraction of C_{max} not bound to plasma proteins; $C_{ss,max}$ Maximum plasma concentration at steady state; CTCAE Common Terminology Criteria for Adverse Events; CV Coefficient of variation; DLT Dose-limiting toxicity; ECG Electrocardiogram; EGF Epidermal growth factor; EGFR Epidermal growth factor receptor; erbB2 Second gene that showed significant similarity to a retroviral oncogene of the avian erythroblastosis virus, also known as human epidermal growth factor (HER2 or HER2/neu); FTKR Flt-1, also known as VEGFR1; glsmean Geometric least-square mean; hERG Human ERG-encoded potassium channel; IC₅₀ Concentration that reduces the effect by 50%; IDEAL Iressa dose evaluation in advanced lung cancer; IV Intravenous; KDR Kinase insert domain protein receptor, also known as VEGFR2 or FLK1; VEGFR Vascular epidermal growth factor receptor; NDA New Drug Application; NSCLC Non-small cell lung cancer; PK Pharmacokinetic; QTc Corrected QT interval; SAE Serious adverse event; SD Standard deviation; SGOT Serum glutamic oxaloacetic transaminase; SGPT Serum glutamate-pyruvate transaminase; t_{max} Time to maximum plasma concentration; $t_{1/2}$ Half-life; Vd Volume of distribution; Vd/F Apparent volume of distribution; VEGFR Vascular epidermal growth factor receptor.

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: April 8, 2015
Requesting Office or Division: Division of Oncology Product 2 (DOP2)
Application Type and Number: NDA 206995
Product Name and Strength: Iressa (Gefitinib) Tablets, 250 mg
Product Type: Single Ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: AstraZeneca
Submission Date: October 3, 2014 and January 26, 2015
OSE RCM #: 2014-2005
DMEPA Primary Reviewer: Davis Mathew, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of NDA 206995 evaluation, this review evaluates the proposed container labels, carton labeling and Prescribing Information (PI) for Iressa Tablets (NDA 206995) for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

Iressa (Gefitinib) was indicated as monotherapy for continued treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) and was approved by the Food and Drug Administration (FDA) in May 5, 2003 as accelerated approval regulations, 21 CFR part 314, subpart H. However, on August 26, 2010 FDA requested that AstraZeneca voluntarily withdraw Iressa due to a failure in postmarketing studies to verify and confirm clinical benefit. Therefore, in a letter dated February 1, 2011 AstraZeneca placed a request for the FDA to withdraw approval of NDA 21399 which was referred to as a business decision on behalf of AstraZeneca.

AstraZeneca submitted NDA 206995 on September 17, 2014 for Iressa seeking approval for a narrower indication for the treatment of patients with (b) (4) metastatic NSCLC whose tumor have EGFR exon 19 deletion or exon 21 substitution mutations as detected by an FDA-approved test.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Upon approval, Iressa will be dosed on the assessment of an FDA-approved test for the detection of EGFR mutation in NSCLC (Non-small cell lung cancer). This FDA-approved test is a

unique addition to the patient selection process which was missing in the previous submissions of Iressa prior to AstraZeneca's voluntary withdrawal.

Our review of FAERS and ISMP did not identify any medication errors. In general, our review found the proposed language used within the PI to be acceptable from a medication error perspective. However, we recommend minor edits to the how supplied/storage and handling section of the PI to improve clarity of information. We also propose the implementation of additional information to patient counseling information (section 17) of the PI to mitigate medication errors. Additionally, our review of the container labels identified areas that can be improved to provide clarity from a safety perspective. We note the absence of units of measurement on the side panel of the container label. We identified additional minor revisions and provide our recommendations in greater detail in section 4 to mitigate medication errors and promote the safe use of this product.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote safe use of the product. We recommend the following to be implemented before the approval of this NDA:

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. We note that the unit of measurement (e.g. °C) is missing immediately following numerical temperature values in section 16 of How supplied/storage and handling within the PI. Revise the PI to include the unit of measurement immediately following numerical temperature values (e.g. 20°C - 25°C (68°F - 77°F)).
2. Section 17 of the PI lacks additional important information that can be beneficial for "Patient counseling Information" purposes. We note the inclusion of the following statements for additional clarity:
 - a. Patients should be informed to avoid CYP3A4 inducers such as St.John's Wort.
 - b. Patients should be advised in the event of a missed dose, they should take it as soon as remembered unless it is within 12 hours of the next dose, in which case advise the patient not to take the missed dose.

4.2 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

A. General Comments (Retail Container and Professional Sample Container)

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 (b) (4) (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.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Iressa that AstraZeneca submitted on January 26, 2015.

Table 2. Relevant Product Information for Iressa	
Initial Approval Date	N/A
Active Ingredient	Gefitinib
Indication	Frist-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) substitution mutations as detected by an FDA-approved test.
Route of Administration	Oral
Dosage Form	Tablets
Strength	250 mg
Dose and Frequency	250 mg orally once daily
How Supplied	Bottles of 30 tablets
Storage	20°C -25°C (68°F - 77°F)

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 30, 2015, we searched the L:drive and AIMS using the terms, Iressa to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous proprietary name review¹ for Iressa, which is not relevant to this labels and labeling review.

¹ Mathew D. Proprietary Name Review for Iressa (IND 120992). Silver Spring (MD):FDA, CDER, OSE, DMEPA (US); 2014 July 21. RCM No.: 2014-17173

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On April 4, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community and Nursing.
Search Strategy and Terms	Match Any of the Words: Iressa, gefitinib

D.2 Results

Our search did not retrieve any results.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on April 1, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter²

Date Range	May 5, 2003 to April 1, 2015
Product	Gefitinib [active ingredient] Iressa [product name]
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Adhesion Issue [PT] Product Compounding Quality Issue [PT] Product Difficult to Remove [PT] Product Formulation Issue [PT] Product Substitution Issue [PT] Inadequate Aseptic Technique in Use of Product [PT]
Country (Derived)	USA

E.2 Results

Our search retrieved 25 cases but after further evaluation, we did not identify any medication error cases relevant for this review that could be addressed by labels and labeling revisions.

E.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

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

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

/s/

DAVIS MATHEW
04/08/2015

CHI-MING TU
04/08/2015

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 206995

Application Type: new NDA

Name of Drug/Dosage Form: Iressa (gefitinib) tablets

Applicant: AstraZeneca UK Limited

Receipt Date: 9-17-2014

Goal Date: 7-17-2015

1. Regulatory History and Applicant's Main Proposals

Iressa received accelerated approval on 5-5-2013 as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. On 6-28-2005, following the results of 3 confirmatory studies, the indication was restricted to use in only those patients already receiving and benefiting from Iressa. In September 2011, the NDA was voluntarily withdrawn.

AstraZeneca conducted additional studies with Iressa in the NSCLC population and has submitted a new NDA for first-line treatment of patients with (b) (4) metastatic 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.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, numerous labeling issues were identified by the clinical review team.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by December 22, 2014. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *Need horizontal line separating the TOC from the FPI*

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *Need white space between the HL Limitation Statement and the product name. Need white space between the initial US approval and INDICATIONS AND USAGE.*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

Selected Requirements of Prescribing Information

• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**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).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- NO** 10. Product title must be **bolded**.

Comment: *Continue bolding of all words in the product title and remove italics.*

Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Need colon after the word "APPROVAL" and periods after the "U" and "S". The words "Initial" and "Approval" are not in all caps.*

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Selected Requirements of Prescribing Information

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *Need the word "Revised".*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
***Comment:** Text needs better alignment.*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- NO** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
***Comment:** Need an asterisk after the word "CONTENTS".*

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment: *Some references are not italicized or have inappropriate commas.*

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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
11/13/2014

MONICA L HUGHES
11/13/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 206995 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: Iressa Established/Proper Name: gefitinib Dosage Form: tablet Strengths: 250 mg		
Applicant: AstraZeneca UK Limited Agent for Applicant (if applicable): AstraZeneca Pharmaceuticals LP		
Date of Application: 9-17-2014 Date of Receipt: 9-17-2014 Date clock started after UN:		
PDUFA Goal Date: 7-17-2015		Action Goal Date (if different):
Filing Date: 11-14-2014		Date of Filing Meeting: 11-10-2014
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input checked="" type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): First line treatment of patients with (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		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <hr/> <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> • <i>The product is a Qualified Infectious Disease Product (QIDP)</i> • <i>A Tropical Disease Priority Review Voucher was submitted</i> • <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input checked="" type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): 54576, 120992

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov:</i>) <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes, answer the bulleted	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

questions below:				
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p>	<input type="checkbox"/>	<input type="checkbox"/>		
If yes, please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, # years requested: 5				
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				

Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Product has Orphan Drug designation for NSCLC.

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

Version: 10/20/2014

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<i>pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT-IRT consult sent 10-29-2014
Meeting Minutes/SPAs	YES	NO	NA	Comment

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 3-11-2014 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11-10-2014

BACKGROUND: Iressa received accelerated approval on 5-5-2013 as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. On 6-28-2005, following the results of 3 confirmatory studies, the indication was restricted to use in only those patients already receiving and benefiting from Iressa. In September 2011, the NDA was voluntarily withdrawn.

AstraZeneca conducted additional studies with Iressa in the NSCLC population and has submitted a new NDA for first-line treatment of patients with (b) (4) metastatic 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.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sharon Sickafuse	Y
	CPMS/TL:	Monica Hughes	N
Cross-Discipline Team Leader (CDTL)	Gideon Blumenthal		Y
Division Director/Deputy	Pat Keegan		Y
Office Director/Deputy	Rick Pazdur		N
Clinical	Reviewer:	Diko Kazandjian Jenny Chang (labeling)	Y Y
	TL:	Gideon Blumenthal	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Robert Schuck Jerry Yu	Y Y

		(Pharmacometrics)	
	TL:	Hong Zhao Liang Zhao (Pharmacometrics)	Y Y
Biostatistics	Reviewer:	Vivian Yuan	Y
	TL:	Kun He	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sachia Khasar	N
	TL:	Whitney Helms	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i>	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Joyce Crich	N
	TL:	Liang Zhou Ali Al-Hakim	Y Y
Biopharmaceutics	Reviewer:	Salah Hamed	Y
	TL:	Angela Dorantes Okpo Eradira covering	N Y
Quality Microbiology	Reviewer:	Robert Mello	N
	TL:		
CMC Labeling Review	Reviewer:	Teicher Agosto	N
	TL:		
Facility Review/Inspection	Reviewer:	Robert Wittorf	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Davis Mathew	Y
	TL:	Chi-Ming (Alice) Tu	N
OSE/DRISK (REMS)	Reviewer:	Mona Patel	Y
	TL:	Naomi Redd	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Lauren-Iacono-Conoor	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:	Robert Schuck (Genomics)	Y
	TL:	Rosane Charlab Orbach	Y
Other attendees	Jennifer Shen, F. Fahnbullah, S.Arora		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIostatISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>IMMUNOGENICITY (protein/peptide products only)</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p>New Molecular Entity (NDAs only)</p> <ul style="list-style-type: none"> Is the product an NME? 	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: No previously uninspected sites</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Richard Pazdur</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"> • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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
11/13/2014