

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211288Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 072775

MEETING MINUTES

Pfizer, Inc.
Attention: Ashok Didolkar, Ph. D.
Director, Worldwide Safety and Regulatory Strategy
235 East 42nd Street
New York, NY 10017

Dear Dr. Didolkar:

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

We also refer to the meeting between representatives of your firm and the FDA on June 13, 2017. The purpose of the meeting was to discuss and reach agreement on the content and format of your proposed New Drug Application (NDA) for dacomitinib for the proposed indication of “the first line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) (b) (4) mutations.”

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

If you have any questions, call me at (301) 796-3074.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: June 13, 2017; 8:30 AM – 10:00 AM, EST
Meeting Location: White Oak Building 22, Room 1315

Application Number: IND 072775
Product Name: dacomitinib
Indication: First-line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) (b) (4) mutations

Sponsor/Applicant Name: Pfizer, Inc.

Meeting Chair: Erin Larkins
Meeting Recorder: Idara Udoh

FDA ATTENDEES

Center for Drug Evaluation and Research (CDER)

Division of Oncology Products 2, Office of New Drugs (OND)

Patricia Keegan, Director

Erin Larkins, Clinical Team Leader

Barbara Sceपुरa, Clinical Reviewer

Idara Udoh, Senior Regulatory Health Project Manager

OND Division of Hematology, Oncology, and Toxicology

Whitney Helms, Nonclinical Supervisor

Office of Pharmaceutical Quality

Joyce Crich, Product Quality Team Leader

Steven Kinsley, Regulatory Business Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology V

Hong Zhao, Clinical Pharmacology Team Leader

Saeho Chong, Clinical Pharmacology Reviewer

Robert Schuck, Clinical Pharmacology Reviewer

Rosane Charlab Orbach, Genomics Team Leader

Office of Biostatistics, Division of Biometrics V (DBV)

Kun He, Biometrics Supervisory Associate Director
Manasi Sheth-Chandra, Biometrics Reviewer

Office of Surveillance and Epidemiology

Division of Risk Management

Mei-Yean Chen, Risk Management Analyst

Division of Medication Error Prevention and Analysis

Latonia Ford, Safety Regulatory Project Manager

Center for Devices and Radiological Health (CDRH)

Office of In Vitro Diagnostics and Radiological Health

Soma Ghosh, Regulatory Scientist
Eunice Lee, Branch Chief

SPONSOR ATTENDEES

Pfizer

Patrice Belanger, PhD Drug Safety Regulatory Strategy Lead
Ashok Didolkar, PhD Global Regulatory Lead
Diana Gernhardt Clinician, Oncology
Nagdeep Giri, PhD Clinical Pharmacology Lead
Rebecca Hintze Programming Therapeutic Area Lead
Charles Mebus, PhD Asset Team Leader
Eric Sbar, DO Global Clinical Lead
Tao Wang, PhD Statistics Lead
Janice Wherry, MD, PhD Safety Risk Lead

Qiagen

Chris Bray Director, Regulatory Affairs, QIAGEN

MEETING PURPOSE

On March 31, 2017, Pfizer, Inc. (“Pfizer”) requested a Type B, pre-NDA meeting to present clinical data from the dacomitinib development plan and to gain FDA concurrence regarding submission of a New Drug Application (NDA) to support approval of dacomitinib for the following proposed indication of “the first line treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)- (b) (4) mutations.”

The briefing package for this meeting was received on May 12, 2017. FDA sent Preliminary Comments to Pfizer on June 9, 2017.

BACKGROUND

Regulatory

On June 20, 2013, Pfizer requested a Type C meeting to discuss the proposed format and content of a future NDA for the proposed indication (b) (4)

Pfizer stated that the NDA would be supported by two major efficacy studies:

- Study A7471009, titled “A Study Of Dacomitinib (PF-00299804) Vs. Erlotinib In The Treatment Of Advanced Non-Small Cell Lung Cancer (ARCHER 1009)”
- Study A7471011, titled “A Double Blind Placebo Controlled Randomized Trial of PF-804 in Patients with Incurable Stage IIIB/IV Non-Small Cell Lung Cancer After Failure of Standard Therapy for Advanced or Metastatic Disease.”

FDA issued written responses only (WRO) on August 19, 2013, in which FDA provided general advice on the content and format of the application, but noted that these written responses did not provide FDA’s formal agreement on the content of a complete application. FDA stated that the discussion regarding the contents of a complete NDA would occur at the time of the pre-NDA meeting, to be held when the summary results for safety and efficacy from Study A7471009 and Study A7471011 were available.

On September 2, 2016, Pfizer requested a meeting to obtain FDA concurrence on the acceptability of their general strategy for the content of the Summary of Clinical Safety (SCS) and ISS due to changes to the clinical development program for dacomitinib. The planned NDA for dacomitinib would seek the proposed indication of “the treatment of patients with (b) (4) metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) (b) (4) mutations.” Since neither Study A7471009 nor Study A7471011 met their primary objectives, the planned NDA would rely primarily on the results of Study A7471050, a randomized, international, open-label, active-controlled study comparing the safety and efficacy of treatment with dacomitinib (45 mg po daily) to treatment with gefitinib for the treatment of patients with NSCLC with EGFR-activating mutations. FDA issued the WRO on September 30, 2016.

On March 31, 2017, Pfizer requested a Type B, pre-NDA meeting to present clinical data from the dacomitinib development plan and to gain FDA concurrence regarding submission of an NDA to support approval of dacomitinib for the following proposed indication (b) (4)

The major efficacy trial supporting the NDA is Study A7471050, entitled “A Randomized, Open-label, Phase 3, Efficacy and Safety Study of Dacomitinib (PF 00299804) versus Gefitinib for the First Line Treatment of

Locally Advanced or Metastatic NSCLC in Patients with Epidermal Growth Factor Receptor Activating Mutation(s).”

Chemistry, Manufacturing, and Controls (CMC)

(b) (4)
[REDACTED]
[REDACTED]. The molecular formula is $C_{24}H_{25}ClFN_5O_2 \cdot H_2O$,
with the corresponding molecular weight of 487.95 Da (monohydrate) (b) (4)
Dacomitinib was developed as an immediate release, blue film-coated tablet containing 15 mg,
30 mg or 45 mg dacomitinib drug substance and predated pharmaceutical excipients. (b) (4)
[REDACTED]

A CMC-Only meeting is scheduled for July 14, 2017.

Nonclinical

Dacomitinib is an irreversible kinase inhibitor targeting the HER2 family kinases including, according to Pfizer, EGFR with exon 19 deletions or exon 21 L858R or T790M mutations. To support the registration of dacomitinib, the nonclinical toxicology package will include the following GLP-compliant studies: a 6-month repeat-dose toxicity study in rats; a 9-month repeat-dose toxicity study in dogs; safety pharmacology studies to assess the effect of dacomitinib on central nervous system, respiratory, and cardiovascular endpoints; genetic toxicology studies (Ames assay, chromosome aberration assay, and an in vivo micronucleus study); and embryo-fetal development toxicity studies in rats and rabbits.

Clinical Pharmacology

Per Pfizer, the pharmacokinetics (PK) of dacomitinib have been evaluated in 18 studies (seven in healthy subjects, six in patients with advanced NSCLC, four in patients with various solid tumors, and one in subjects with impaired hepatic function. Overall results are summarized below:

- a) PK of dacomitinib is similar in healthy subjects and patients with NSCLC. The systemic exposures (C_{max} and AUC) of dacomitinib increased proportionally with doses tested (0.5 mg to 60 mg QD) with the time to reach the maximum plasma concentration (T_{max}) occurring at approximately 6 hours. The elimination half-life ($t_{1/2}$) ranged from 54 to 80 hours following oral administration of dacomitinib to patients with solid tumors. After daily oral dose of 45 mg for 14 days, mean AUC accumulation of dacomitinib in patients ranged from 5.7 to 6.4 fold.
- b) A mean absolute oral bioavailability of dacomitinib is 80%. A high-fat, high-calorie meal increased mean dacomitinib AUC and C_{max} by 14% and 24%, respectively when compared to fasted condition.

- c) Proton-pump inhibitors (e.g., rabeprazole) decreased mean dacomitinib AUC_{inf} and C_{max} by 29% and 50%, respectively. Local antacids (aluminum hydroxide/magnesium hydroxide/simethicone liquid [400 mg/5 mL, Maalox® Maximum Strength]) had no effect on C_{max} and AUC_{inf} of dacomitinib. The effect of H_2 -receptor antagonists on the plasma concentrations of dacomitinib is unknown.
- d) Human plasma protein binding of dacomitinib and its metabolite, PF-05199265, is approximately 98% and >99%, respectively. Volume of distribution ranged from 2292 to 4005 L.
- e) Dacomitinib-related components are primarily eliminated via the fecal route. Following oral administration of a single dose of [^{14}C]dacomitinib, approximately 79% and 3% of the administered radioactive dose were recovered in feces and in urine, respectively.
- f) Following oral administration of a single dose of [^{14}C]dacomitinib, unchanged dacomitinib is the predominant radiolabeled component in plasma. Dacomitinib undergoes oxidative metabolism and glutathione conjugation. Oxidative metabolism of dacomitinib involves CYP2D6 for the formation of O-desmethyl dacomitinib (PF-05199265) and CYP3A (formation of other minor oxidative metabolites).
- g) A formal renal impairment study has not been conducted. However, in a population pharmacokinetic (PopPK) analysis performed with available data (N=1078), creatinine clearance was not identified as an important covariate influencing the PK of either dacomitinib or PF-05199265.
- h) Dacomitinib or PF-05199265 is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A activities in human liver microsomes. However, dacomitinib and PF-05199265 inhibited CYP2D6 activity and may have the potential for a clinically relevant drug-drug interaction (DDI) with concomitantly administered CYP2D6 substrates.
- i) Dacomitinib did not induce CYP3A, CYP1A2 or CYP2B6 in cryopreserved human hepatocytes at concentrations of >50 times the unbound C_{max} observed in humans after oral administration of multiple doses of 45 mg QD.
- j) Dacomitinib exposure following a single dose was increased 37% when co-administered with paroxetine, a strong inhibitor of CYP2D6, indicating that the contribution of CYP2D6 to the overall clearance of dacomitinib is likely to be modest.
- k) Subjects with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment have similar PK compared to subjects with normal hepatic

function. Dacomitinib has not been studied in subjects with severe (Child- Pugh Class C) hepatic impairment.

- l) Collective data indicated no significant drug-related QT interval prolongation at plasma exposures reflective of 45 mg QD dosing (recommended dose).

Clinical

Pfizer reports that, as of July 29, 2016, 2137 patients have been treated with dacomitinib, administered either as a single agent (n=1964) or in combination with another drug (n=173), in 17 clinical trials. This includes 1473 patients with NSCLC who received dacomitinib administered as a single agent at a dose of 45 mg once daily (QD). Among these 1473 NSCLC patients, 394 of these patients were known to have tumors harboring EGFR-activating mutations, while 256 had received no prior treatment for advanced / metastatic NSCLC.

Pfizer proposes to include data from five studies to support the efficacy of dacomitinib in the proposed NDA. Table 1 includes a brief description of these studies and their results.

Table 1: Studies proposed for inclusion in the NDA to support efficacy

Study Number	Title / Study Design	Results
Primary Efficacy Trial		
Study A7471050 "1050"	Title: A Randomized, Open-label, Phase 3, Efficacy and Safety Study of Dacomitinib (PF 00299804) versus Gefitinib for the First Line Treatment of Locally Advanced or Metastatic NSCLC in Patients with Epidermal Growth Factor Receptor Activating Mutation(s) Eligibility: Patients with EGFR-mutation positive NSCLC (exon 19 or L858R) Randomization (1:1); Stratification factors: • Race: Japanese vs. Mainland Chinese vs. Non-East Asian; • EGFR-activating mutation: exon 19 vs. L858R Primary endpoint: PFS by BIRC according to RECIST v1.1	Efficacy dataset of 452 patients randomized to dacomitinib 45 mg (n=227) or gefitinib 250 mg daily (n=225). Safety population 451 (1 patient randomized to gefitinib was not treated) Significant improvement in PFS with a hazard ratio [HR] of 0.589 [95% confidence interval (CI): 0.469, 0.739]; p-value <0.0001, 1-sided, stratified log-rank. The median PFS was 14.7 months (95% CI: 11.1, 16.6) in the dacomitinib arm and 9.2 months (95% CI: 9.1, 11.0) in the gefitinib arm ORR was 75% vs. 72% for dacomitinib and gefitinib, respectively
Supportive Studies		
Study A7471017 "1017"	Title: A Phase 2, Open Label, Single-Arm Trial of Dacomitinib in Selected Patients with Advanced Adenocarcinoma of the Lung Eligibility in Cohort A: previously untreated NSCLC Starting dose of 45 mg or 30 mg; Patients who initiated dacomitinib at 30 mg/day underwent escalation to 45 mg/day Single arm; no randomization/ stratification	A total of 89 patients enrolled in Cohort A, which included 45 patients with activating EGFR mutations (exon 19, n=25; exon 21, n=20) <u>EGFR Positive Subset of Cohort A</u> The ORR was 76% (95% CI: 61, 87) and the median DOR was 17.2 months (95% CI 11.8, 23.0)

Study Number	Title / Study Design	Results
	PFS rate at 4 months	
Study A7471009 "1009"	A Randomized Double Blind Phase 3 Efficacy and Safety Study of PF-00299804 (Dacomitinib) versus Erlotinib for the Treatment of Advanced Non-Small Cell Lung Cancer Following Progression After, or Intolerance to, at Least One Prior Chemotherapy Advanced NSCLC after 2 prior regimens 2 cohorts: NSCLC, and NSCLC KRAS wild-type Primary endpoint: PFS by BIRC Stratification factors: histology, race, ECOG PS, smoking status	A total of 878 were randomized to dacomitinib (n=439) or erlotinib (n=439). The safety (as treated) population is 872 patients. No significant difference in PFS [HR 0.941(95% CI: 0.802, 1.104); p-value 0.458, 2-sided]. The median PFS was 2.6 months in both arms. In an exploratory subset analysis of 76 patients with NSCLC bearing "EGFR-activating" mutations, the observed HR favored the dacomitinib arm [HR 0.670 (95% CI: 0.367, 1.222)]. The KM-estimated median PFS was 14.6 months for dacomitinib-treated patients and 9.6 months for erlotinib-treated patients.
Study A7471028 "1028"	Title: A Randomized Phase 2 Trial of Dacomitinib Versus Erlotinib for the Treatment of Advanced Non-Small Cell Lung Cancer After Failure of at Least One Prior Chemotherapy Regimen Eligibility: advanced NSCLC with 1-2 prior treatments Stratification factors: • Race • histology • smoking status Primary endpoint: PFS by Investigator	A total of 188 patients were randomized to dacomitinib 45 mg (n=94) or erlotinib 150 mg (n=94) There was a statistically significant, but clinically modest improvement in investigator-assessed PFS, favoring dacomitinib [HR 0.657 (95% CI: 0.472, 0.914); p = 0.012, two-sided]. The median PFS was 2.8 months (95% CI: 1.9, 3.47) in the dacomitinib arm and 1.9 months (95% CI: 1.8, 2.69) in the erlotinib arm. In an exploratory subgroup analysis of 25 patients with NSCLC bearing "EGFR-activating mutations," the observed hazard ratio favored the dacomitinib arm [HR 0.414 (95% CI: 0.156-1.099)]. The KM-estimated median PFS was 16.1 months in dacomitinib-treated patients and 7.4 months in erlotinib-treated patients.
Study A7471011 "1011"	Title: A Phase 3, Double-Blind, Placebo-Controlled, Randomized Trial of PF- 00299804 in Patients with Incurable Stage IIIB/IV Non-Small Cell Lung Cancer After Failure of Standard Therapy for Advanced or Metastatic Disease Eligibility: Refractory NSCLC No stratification factors listed Primary endpoint: overall survival	A total of 720 patients were randomized (2:1) to dacomitinib (n=480) or placebo (n=240) There was no evidence of an effect on overall survival [HR 1.003 (95% CI: 0.829, 1.214); p= 0.510, 1-sided, stratified log-rank test] with dacomitinib treatment. The median survival was 6.8 months in the dacomitinib arm and 6.3 months in the placebo arm. In an exploratory subset analysis of 135 patients with NSCLC bearing "EGFR-activating" mutations, with or without a T790M mutation, there was no evidence of an effect on overall survival as compared to placebo [HR 0.905 (95%CI: 0.618, 1.326)] with KM-estimated median survival of 7.5 months in the dacomitinib arm and 8.1 months in the placebo arm.

Pfizer describes Study 1050 as the "pivotal study" to support the NDA. Data from Cohort A of Study 1017 would provide supportive efficacy data in the proposed indication (first-line treatment), while the other studies would provide additional supportive efficacy data (b) (4)

Study 1050 is an ongoing, randomized, open-label, multicenter study of dacomitinib versus gefitinib as first-line treatment in 452 patients with advanced or metastatic NSCLC harboring EGFR-activating mutation. The primary efficacy outcome measure is progression-free survival (PFS) as determined by blinded independent radiology committee/ independent review committee (IRC) using RECIST v1.1. Overall survival (OS) is a key secondary endpoint. All eligible patients had tumors that tested positive for one of the two most common EGFR-activating mutations (exon 19 deletion or L858R substitution mutation in exon 21); patients with T790M mutation in exon 20 were eligible. The test used to determine EGFR mutation status was the Qiagen *therascreen*[®] EGFR RGQ PCR Kit. All eligible patients had to have adequate renal, hepatic, and hematologic function, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Patients were randomized 1:1 to receive either dacomitinib 45 mg QD or gefitinib 250 mg QD. Randomization was stratified by race (Japanese vs. mainland Chinese vs. other East Asian vs. non-East Asian) and EGFR-activating mutation (exon 19 deletion vs. exon 21 L858R).

Pfizer presents topline results for Study 1050 in the meeting package. The median PFS per IRC review was 14.7 months (95% CI: 11.1, 16.6) in the dacomitinib arm versus 9.2 months (95% CI: 9.1, 11.0) in the gefitinib arm. The overall response rate (ORR) by IRC was similar between arms, 75% and 72% for the dacomitinib and gefitinib arms, respectively. The median duration of response (DoR) in the dacomitinib arm was 14.8 months (95% CI: 12.0, 17.4) compared to 8.3 months (95% CI: 7.4, 9.2) in the gefitinib arm.

The adverse event (AE) profile for dacomitinib is similar to currently approved EGFR tyrosine kinase inhibitors (i.e., erlotinib, gefitinib). The most common AEs associated with dacomitinib are gastrointestinal (GI) toxicities, skin and nail toxicities, and constitutional adverse events. In Study 1050, discontinuation due to treatment-emergent AEs (TEAE) was higher in the dacomitinib arm (18%) compared to the gefitinib arm (12%). The types of AEs were similar between the study arms, but the incidence of several toxicities known to be associated with EGFR inhibitors, specifically diarrhea, rash, and nail toxicity, were higher in the dacomitinib arm.

Pfizer proposes that the organization of the Summary of Clinical Safety (SCS) for the planned NDA focus on safety data from the indication population, supplemented by safety information from other lines of therapy and from a broader NSCLC population, both those with NSCLC with EGFR-activating mutations and NSCLC independent of EGFR-activating mutation status. Pfizer proposes inclusion of data from the following studies in the SCS:

- a) Study 1050 (first-line NSCLC patients with EGFR-activating mutations [full characterization])
- b) Study 1017 (Cohort A which includes NSCLC patients with EGFR-activating mutations receiving dacomitinib 45 mg starting dose [key data to be included])
- c) Studies 1009 and 1011 (later-line unselected NSCLC patients [key safety data: key tables in SCS appendix and full tables in CSRs])

- d) Pool A: Pooled single-agent 45 mg, NSCLC patients with EGFR-activating mutation (N=394 [full characterization])
- e) Pool B: Pooled single-agent 45 mg, patients with NSCLC with or without EGFR-activating mutations (N=1473 [key safety data: full table sets in SCS appendix])
- f) Completed clinical studies with other dacomitinib dosing regimens and/or indications (reference to CSRs for details plus any significant individual case information to be described)
- g) Clinical pharmacology studies (brief mention and reference to CSRs for details) plus any significant individual case information to be described
- h) Ongoing clinical studies, investigator-initiated research clinical studies, compassionate use, and/or studies of dacomitinib plus other study drugs (serious adverse events (SAEs) and deaths from Pfizer Global Safety Database)

Center for Devices and Radiological Health (CDRH)

The central test for Study 1050 was the QIAGEN *therascreen*® EGFR RGQ PCR Kit, a real-time PCR test for the qualitative detection of EGFR gene mutations in DNA derived from formalin-fixed paraffin-embedded NSCLC tumor tissue. However, several clinical trial assays (CTAs) were used for patient enrollment in Study 1050. A bridging study is required to compare the results generated using the CTAs with the proposed companion diagnostic test, the QIAGEN *therascreen*® EGFR RGQ PCR Kit. The test is already approved for afatinib and gefitinib indications.

DISCUSSION OF FDA RESPONSES TO SPONSOR QUESTIONS

Nonclinical

Pfizer's position on Question #1 provided on page 54 of briefing package.

1. **Does the Agency concur that the nonclinical toxicology studies conducted are sufficient to support approval of dacomitinib from a nonclinical toxicology perspective?**

FDA Response: The nonclinical toxicology studies appear sufficient to support the filing of an NDA submission; however, the acceptability of data from these studies will be determined during review of all data included in the NDA submission.

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement.

Discussion During Meeting: No discussion occurred.

Clinical Pharmacology

Pfizer's position on Question #2 provided on page 54-55 of briefing package.

2. **Pfizer proposes to present population PK analyses regarding impact of renal function based on calculated creatinine clearance that will provide guidance for labeling regarding use of dacomitinib in subjects with renal impairment. Does the Agency agree with Pfizer's approach?**

FDA Response: Yes, FDA generally agrees with the proposed approach as the renal elimination appears to be a minor route of the overall systemic clearance of dacomitinib and its metabolite. The adequacy of the data and analyses included in the planned NDA submission will be assessed during the review of the NDA.

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement.

Discussion During Meeting: No discussion occurred.

Pfizer's position on Question #3 provided on page 55 of briefing package.

3. **Pfizer plans to provide exploratory analysis of exposure–response (efficacy and safety) including data from Study 1050. Relevant reports will be presented as standalone documents in Module 5. Does the Agency agree with Pfizer's approach?**

FDA Response: Yes, the proposed approach appears to be acceptable. The adequacy of the data and analyses included in the planned NDA submission will be assessed during the review of the NDA. See additional clinical pharmacology comments.

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement.

Discussion During Meeting: No discussion occurred.

Clinical

4. **Does the Agency concur with Pfizer's proposal regarding inclusion of copies of individual case report forms in the planned New Drug Application?**

FDA Response: Yes, FDA agrees with Pfizer's proposal to include copies of case report forms for all patients on completed studies (defined as studies with the final Clinical Study Report will be available at the time of NDA submission) who:

- died within 28 days after the last dose of protocol-specified treatment;
- died >28 days after the last dose of protocol-specified treatment where the death is considered related to the study treatment; or
- discontinued treatment due to a treatment-emergent adverse event (TEAE).

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement.

Discussion During Meeting: No discussion occurred.

Pfizer's position on Question #5 (Support for Proposed Indication) provided on pages 56-58 of briefing package.

5. **Does the Agency concur that the efficacy data from Studies 1050 and 1017 and safety information from 1964 patients with NSCLC receiving dacomitinib as a single agent, as briefly summarized below, are adequate to support regular approval of dacomitinib for the proposed indication?**

FDA Response: The efficacy data proposed for inclusion in the NDA, which will include data from Study 1050, Cohort A of Study 1017, and data from Studies 1009, 1028, and 1011 appear adequate to support filing. Please note that the efficacy results of the intent-to-treat population (or 'as treated' for Cohort A of Study 1017) should be summarized as well as the exploratory subset analyses conducted in patients with NSCLC harboring an EGFR exon 19 deletion or an EGFR exon 21 L858R mutation. The adequacy of the proposed data to support approval will be determined at the time of the review.

Please note that an NDA is required to contain a summary of the application in enough detail that the reader may gain a good general understanding of the data and information in the application, including an understanding of the quantitative aspects of the data. Furthermore, the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) are not summaries but rather detailed integrated analyses of all relevant data from the clinical study reports that belong in Module 5. FDA considers the ISE and ISS critical components of the clinical efficacy and safety portions of a marketing or licensing application on. Therefore, the ISE and ISS are required in applications submitted to the

FDA in accordance with the regulations for NDA submissions (21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)(a) , respectively).

In general, positive results from two randomized controlled studies are required for marketing approval. FDA will accept the results of a single adequate and well-controlled trial to support marketing approval if the trial shows a clinically meaningful, statistically significant effect that is internally consistent across relevant subgroups. The results of the single trial must be sufficiently robust and so compelling that it would be unethical to repeat the study. For further information please refer to the FDA document “Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products,” available at <http://www.fda.gov/cder/guidance/index.htm>.

Pfizer’s Response (provided via email 6/12/2017): Pfizer would like to reconfirm the 2013 Agency agreement regarding the briefing package including Appendix 1, which detailed the presentation of the SCS; however, there will be some necessary modifications due to change in proposed indication and pooling strategy.

Discussion During Meeting: The proposal for submission of safety data in which the following pooled datasets will be provided is acceptable:

- Clinical trial databases
 - First line NSCLC with EGFR-activating mutations
 - Pool A: NSCLC with EGFR-activating mutations
 - Pool B: 10 completed trials in patients with NSCLC (irrespective of mutations)
- Global safety database with SAEs in investigator-sponsored trials and expanded access experience.

The SCS will summarize the incidence of SAEs across all trials and global safety experience, with hyperlinks to individual CSRs containing patient narratives or to patient narratives for expanded access experience in Module 5.

In the SCS, side-by-side comparison of AEs will be provided only for the randomized trials, Studies 1050, 1009, 1028, and 1011. With regard to key safety data, FDA requested, and Pfizer agreed to provide, information on patients who discontinue or modify the dose of dacomitinib for an AE, as well as TEAEs, deaths, and SAEs.

Pfizer’s position on Question #6 (Safety Data Cutoff Date) provided on page 58 of briefing package.

6. Does the Agency concur with Pfizer’s planned data cutoff dates for initial NDA submission and 4-month safety update as described in the meeting package?

FDA Response: FDA has no objections to the proposed data cutoff. FDA agrees with the proposal that the 120-day safety update will be limited to new safety information

obtained in Study 1050. Given the extensive clinical experience in more than 1000 dacomitinib-treated patients, the safety updates should be limited to new serious adverse events (SAEs) and relevant updates on previously reported SAEs.

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement.

Discussion During Meeting: No discussion occurred.

Pfizer's position on Question #7 (Summary of Clinical Safety) provided on pages 58-59 of briefing package.

7. **Given that the primary focus of the Summary of Clinical Safety (SCS) is to support the first-line treatment of EGFR-activating mutation-positive NSCLC patients with 45 mg daily doses of dacomitinib, does the Agency agree with the proposed presentation of safety data in the SCS as described in the meeting package?**

FDA Response: The SCS should contain side-by-side comparisons of safety in all randomized trials. Additionally, an assessment of safety data should be provided by individual and pooled safety data across single-arm studies in which dacomitinib was administered at 45 mg daily as a single agent across the "as-treated" study population, as well as in the subsets of patients with "EGFR-activating" mutations. Inclusion in the pooled dataset of safety data from the dacomitinib arm in randomized studies alone with single arm study safety data is acceptable. For all safety datasets, characterize the duration of exposure based on the number and proportion of patients exposed to dacomitinib for 6 months or longer and those exposed to dacomitinib for 12 months or longer. Assessment of safety should not be limited to studies with NSCLC for the characterization of serious adverse reactions; rather it should be based on SAEs observed in the 23 completed studies enrolling more than 2000 dacomitinib-treated patients. Please clarify the definition of "key data" as it relates to the proposal for inclusion of data in the SCS.

Pfizer's Response (provided via email 6/12/2017): The Sponsor understands and concurs with the Agency's clarifications regarding the proposed presentation of safety data in the SCS as follows:

FDA verbatim request	Synopsis of FDA request	Sponsor response
Side-by-side comparisons of safety in all randomized trials.	Side by side safety tables with both treatment arms for three Phase 3 studies (1009, 1011, 1050)	Agreed for Phase 3 trials 1009 1011, and 1050: including selected parameters: TEAE, SAE, deaths. A smaller Phase 2 randomized trial (Study 1028) will not be included as a side-by-side comparison because the trial design and safety results are similar to Study 1009. The data for Study 1028 are included as appropriate in the pooled datasets.

FDA verbatim request	Synopsis of FDA request	Sponsor response
Assessment of safety data should be provided by individual and pooled safety data across single-arm studies in which dacomitinib was administered at 45 mg daily as a single agent across the “as-treated” study population, as well as in the subsets of patients with “EGFR-activating” mutations.	Include: - Pool A safety analysis needed - Pool B safety analysis needed	Agreed - Pool A: full characterization: full characterization: all causality and related TEAEs, Deaths, SAEs, permanent treatment discontinuations and treatment modifications associated with AEs, AEs of Special Interest, laboratory test results, intrinsic/extrinsic factors - Pool B: NSCLC: key parameters: TEAEs, Deaths, SAEs
Inclusion in the pooled dataset of safety data from the dacomitinib arm in randomized studies alone with single arm study safety data is acceptable.	Agree with pools as described	Acknowledged
For all safety datasets, characterize the duration of exposure based on the number and proportion of patients exposed to dacomitinib for 6 months or longer and those exposed to dacomitinib for 12 months or longer.	Provide the number and proportion of patients exposed to dacomitinib for ≥ 6 months and those exposed to dacomitinib for ≥ 12 months in Pool A and Pool B.	Agreed
Assessment of safety should not be limited to studies with NSCLC for the characterization of serious adverse reactions; rather it should be based on SAEs observed in the 23 completed studies enrolling more than 2000 dacomitinib-treated patients.	Provide SAE data for other studies beyond pivotal and Pools	Agreed
Please clarify the definition of “key data” as it relates to the proposal for inclusion of data in the SCS.	Define “key data” parameters	Agreed

Additionally, Pfizer would like to update the Agency on the revision to the proposed presentation of SCS.

Rationale for update to the patient description categories for the Summary of Clinical Safety

(b) (4)

This pool is comprised of data from patients of the dacomitinib arm of Study 1050 and those in Study 1017 Cohort A who received a starting dose of 45 mg QD and is appropriately entitled “First-Line Activating Mutation Pool”. In recognition of the relevance of this pool to understanding the safety for the indication, this pool is now one of the cohorts within the Key supportive data along with moving a slightly broader pool, Pool A, a 5 study pool of patients (NSCLC with EGFR-activating mutations), to the Key supportive data category.

Briefing Document May 8 2017	Current SCS	
	Populations	Studies, Cohorts, and Pools
Pivotal safety data Phase 3 Study 1050 Full characterization	Pivotal data	Phase 3 Study 1050 First-line NSCLC patients with EGFR-activating mutations, single-agent dacomitinib 45 mg QD starting dose, full characterization: all causality and related TEAEs, Deaths, SAEs, permanent treatment discontinuations and treatment modifications associated with AEs, AEs of Special Interest, laboratory test results, intrinsic/extrinsic factors
Supportive first-line cohort: Study 1017 Cohort A, NSCLC EGFR-activating mutations dacomitinib 45 mg starting dose Key safety data	Key supportive data	Now called: Study 1017 Activating Mutation Cohort First-line NSCLC from Cohort A, EGFR-activating mutations, dacomitinib single-agent 45 mg, limited characterization: TEAEs, TRAEs, Deaths, SAEs, laboratory test results
		First-Line Activating Mutation Pool: First-line NSCLC, EGFR-activating mutations, single-agent dacomitinib 45 mg QD, key safety parameters; all causality and related TEAEs, ADRs, Deaths, SAEs, permanent treatment discontinuations and treatment modifications associated with AEs, laboratory test results
		Any-Line Activating Mutation Pool, "Pool A" NSCLC EGFR-activating mutations, single-agent dacomitinib 45 mg QD, full characterization, same as for Study 1050
Supportive safety data Phase 3 studies: Studies 1009 and 1011: later-line unselected NSCLC patients Key safety data tables in SCS appendix, full table sets in CSRs Pool A: Pooled single-agent 45 mg, NSCLC patients with EGFR-activating mutation Full characterization Pool B: Pooled single-agent 45 mg, patients with NSCLC with or without EGFR-activating mutations Key safety data: full table sets in SCS appendix	Additional supportive data	Phase 3 Study 1009, and Study 1011, Key safety parameters: TEAEs, Deaths, SAEs, full tables in CSRs
		No longer part of additional supportive data, now in key supportive data
		All NSCLC Pool (10 studies) "Pool B" NSCLC, dacomitinib 45 mg QD, Key safety parameters: TEAEs, Deaths, SAEs

Briefing Document May 8 2017	Current SCS	
	Populations	Studies, Cohorts, and Pools
Completed clinical studies with other dacomitinib dosing regimens and/or indications (reference to CSRs for details plus any significant individual case information to be described)		Characterization of deaths, SAEs, and permanent discontinuations due to TEAEs; full tables in CSRs
Additional supportive safety data (by study)	Additional supportive data	
Clinical pharmacology studies: brief mention plus any significant individual case information; CSRs for details		Characterization of deaths, SAEs, and permanent discontinuations due to TEAEs; full tables in CSRs
Ongoing clinical studies, Investigator Initiated Research studies, compassionate use, and/or dacomitinib combination study (SAEs and deaths from Pfizer Global Safety Database)		Characterization of deaths and SAEs, from data available in Pfizer Global Safety database

Discussion During Meeting: Refer to Discussion During Meeting for Question #5.

Pfizer's position on Question #8 (Safety Narrative Plan) provided on pages 59-61 of briefing package.

8. Does the Agency concur with Pfizer's revised proposal regarding inclusion of patient safety narratives in the New Drug Application submission?

FDA Response: Pfizer's proposal regarding inclusion of patient safety narratives in the NDA is acceptable.

Please note that narrative summaries should not merely provide, in text format, the data that are already presented in the case report tabulation, as this adds little value. A valuable narrative summary would provide a complete synthesis of all available clinical data and an informed discussion of the case, allowing a better understanding of what the patient experienced. The following is a list of components that would be found in a useful narrative summary: patient age and gender, signs and symptoms related to the AE being discussed, an assessment of the relationship of exposure duration to the development of the AE, pertinent medical history, concomitant medications with start dates relative to the AE, pertinent physical exam finds, pertinent test results (e.g., lab data, ECG data, biopsy data), discussion of the diagnosis as supported by available clinical data, for events without a definitive diagnosis, a list of the differential diagnoses, treatment provided, re-challenge results (if performed), outcomes and follow-up information.

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement and would like to assure the Agency that patient safety narratives will provide a complete synthesis of all available clinical data regarding individual patient and an informed discussion of the case, allowing a better understanding of what the patient experienced.

Discussion During Meeting: FDA acknowledged Pfizer's response; no further discussion occurred.

Pfizer's position on Question #9 (Data Sets) provided on pages 61-62 of briefing package.

9. **Does the Agency agree with Pfizer's proposal regarding the format of datasets to be included in the planned NDA?**

FDA Response: FDA agrees with Pfizer's proposal to provide datasets for clinical trials and pooled safety in the form of Analysis Data Model (ADaM) datasets and to submit datasets (.xpt) for individual studies (Studies 1050, 1009, and 1011) in Clinical Data Interchange Standards Consortium (CDISC) (Study Data Tabulation Model [SDTM] and ADaM) format, including annotated case report forms (CRFs) and define.pdf/xml files. However, please confirm submission and format of datasets for Study 1017. Please ensure that demographic datasets have a single entry per subject enrolled in the study (or pooled studies).

Pfizer's Response (provided via email 6/12/2017): The CSR for 1017 was completed in legacy Pfizer data standards and the sCSR was completed in CDISC. Both sets of data will be provided in the submission. The CSR will include analysis datasets in the legacy Pfizer data standard and the sCSR will include cumulative data in CDISC, so will include SDTM and ADaM datasets. Also, Pfizer confirms that the demographic or ADSL datasets will have a single entry per patient enrolled in the study (or patients within pooled population).

Discussion During Meeting: FDA stated that Pfizer's proposal is acceptable.

Pfizer's position on Question #10 (Tumor Assessment Image Format) provided on pages 62-63 of briefing package.

10. **Does the Agency concur with Pfizer's proposals regarding: a) the timing of radiographic image submission and b) the radiographic images being provided in Digital Imaging and Communications in Medicine format?**

FDA Response: FDA does not require images to be submitted with the NDA. Pfizer should provide radiographic images to FDA upon request. DICOM format is acceptable.

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement.

Discussion During Meeting: No discussion occurred.

Pfizer's position on Question #11 (Priority Review) provided on page 63 of briefing package.

11. **Does the Agency concur with Pfizer's proposal that the NDA for dacomitinib for the proposed indication should be granted a priority review designation?**

FDA Response: Determination of review designation is made at the time of the NDA submission.

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement.

Discussion During Meeting: No discussion occurred.

EGFR Companion Diagnostic

Pfizer's position on Question #12 provided on page 63 of briefing package.

12. **QIAGEN would be in a position to share a high-level summary of the bridging study data at the time of pre-NDA meeting. Would CDRH be able to provide comments at that time regarding suitability of data in terms of being supportive of the Premarket Approval Supplement approval?**

FDA Response: CDRH will not be able to provide feedback on the suitability of the bridging study results and analysis during the June 13, 2017 meeting. FDA requested that QIAGEN submit the high level summary of the data in a pre-submission for CDRH review and feedback.

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement. Qiagen will submit the high level summary of the data in the Pre-Submission for CDRH review and feedback.

Discussion During Meeting: No discussion occurred.

Pfizer's position on Question #13 provided on page 64 of briefing package.

13. **In the scenario where the NDA receives Priority Review designation, could CDRH comment on whether this allows for timely review of the Premarket Approval Supplement in line with the Drug Action date?**

FDA Response: If the PMA supplement is submitted within two weeks of the NDA submission, as indicated by Pfizer, CDRH will coordinate the action date of the PMA supplement along with the NDA submission.

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement.

Discussion During Meeting: No discussion occurred.

Waiving the NDA User Fee

Pfizer's position on Question #14 provided on page 64 of briefing package.

14. **Based on the orphan designation for dacomitinib for the proposed indication, Pfizer understands that the NDA User Fee will be waived for the NDA of dacomitinib for the proposed indication. Does the Agency concur with Pfizer's understanding?**

FDA Response: Yes, the user fee is waived for the specific indication for which the orphan designation has been granted.

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement.

Discussion During Meeting: No discussion occurred.

ADDITIONAL FDA COMMENTS

Clinical

15. Product labeling should describe all statistical results using two-sided test(s).

Pfizer's Response (provided via email 6/12/2017): In the product labeling Pfizer will describe all statistical results using two-sided test(s).

Discussion During Meeting: No discussion occurred.

Clinical Pharmacology

16. In the planned NDA submission, provide all available germline genotype data from dacomitinib trials, including but not limited to variants in CYP2D6. The submitted dataset(s) should include individual genotypes, inferred phenotypes and linkage to demographic and clinical data, as well as pharmacokinetic data. Also provide information on the genotyping method used and the list of alleles tested.

Pfizer's Response (provided via email 6/12/2017): Germline genotyping was performed for subjects in 5 healthy volunteer studies, 1 phase 2 patient study 1042 and in a subset of patients in phase 3 Study 1050. Pfizer will provide data requested by the agency as available from these studies.

Discussion During Meeting: No discussion occurred.

17. In the planned NDA submission, address the following questions in the Summary of Clinical Pharmacology:
- a) What is the basis for selecting the doses and dosing regimen used in the trials intended to support the marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dosage and administration.
 - b) What are the exposure-response relationships for efficacy, safety and biomarkers? Provide a justification for the exposure metrics that are used in the exposure-response analyses with special consideration of the high rate of dose reduction and interruption with dacomitinib.
 - c) What is the effect of dacomitinib on QT/QTc interval?
 - d) What are the characteristics of absorption, distribution, and elimination (metabolism and excretion) of dacomitinib?

- e) What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for the recommendation with regard to meals or meal types.
- f) How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, body weight, disease, and organ dysfunction) influence the exposure, efficacy, or safety of dacomitinib? What dose modifications are recommended?

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement and would like to assure the Agency that the Summary of Clinical Pharmacology will discuss above topics.

Discussion During Meeting: No discussion occurred.

18. In the planned NDA submission, apply the following advice in preparing the clinical pharmacology sections:
- a) Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
 - b) Provide a final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean $\pm$ standard deviation) and median with minimum and maximum values as appropriate.
 - c) Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
 - d) Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - e) Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement and would like to assure the Agency that the submission will include the above information.

Discussion During Meeting: No discussion occurred.

19. Refer to the following guidance for general expectations on submitting pharmacometrics data and models:

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement and assure the Agency that the guidance above will be referred for submission of pharmacometric data and models.

Discussion During Meeting: No discussion occurred.

20. Submit study reports of population pharmacokinetics analyses (popPK) and exposure-response (measures of effectiveness, biomarkers and toxicity) relationship analyses in the targeted patient population. Refer to the Guidances for Industry available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> for popPK analyses and <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf> for exposure-response relationship analyses.

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement. Pfizer plans to submit reports of PopPK analysis and exposure-response relationship analyses in the submission.

Discussion During Meeting: No discussion occurred.

21. With regards to the physiologically-based pharmacokinetic (PBPK) submission:
- a) Include the purpose of the simulations, assumptions, detailed process of PBPK model building and verification, a summary of model input parameters, version of software, simulation results, and conclusions in the study report.
 - b) Provide the study report as PDF files (screenshots can be incorporated if required).
 - c) Include the model files used to generate the final PBPK simulations. These files should be executable by FDA reviewers using the specified software.
 - d) Include appropriate supporting documentations such as any special instructions and file definitions.

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement. Pfizer will follow above advisement for any PBPK modeling reports and models submitted.

Discussion During Meeting: No discussion occurred.

22. Include the following items in the QT study report:

- a) Electronic copy of the study report
- b) Electronic or hard copy of the clinical protocol
- c) Electronic or hard copy of the Investigator's Brochure Annotated CRF
- d) A data definition file which describes the contents of the electronic data sets
- e) Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
- f) Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
- g) Data set whose QT/QTc values are the average of the above replicates at each nominal time point
- h) Narrative summaries and case report forms for any:
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure
 - vi. Adverse events resulting in the subject discontinuing from the study
- i) ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- j) A completed Highlights of Clinical Pharmacology Table

Pfizer's Response (provided via email 6/12/2017): We acknowledge the Agency's advisement. Pfizer will follow the above advisement on QTc reports regarding data, ECG waveform and supportive documents.

Pfizer will provide narratives for Study 1047 as agreed in response to Question 8. Similarly, Pfizer will provide copies of individual patient CRFs as agreed in response Question 4 for study 1047.

Discussion During Meeting: FDA stated that Pfizer's proposal was acceptable with the following exception: CRFs must be provided for all patients enrolled in Study 1047 for

all patients who contributed to the QTc assessments. Pfizer agreed to provide all CRFs for all such patients enrolled in that study.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The following captures agreements for all disciplines except CMC.

- The content of a complete application for all disciplines except CMC was discussed.
 - Pfizer stated that the application will include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion on the need for REMS occurred. Based on the information provided in the pre-meeting package, the Office of New Drugs and the Office of Surveillance and Epidemiology agree that inclusion of Risk Mitigation and Evaluation Strategies (REMS) is not required in the initial NDA submission for the purposes of filing. FDA will make a final determination regarding the need for REMS during the review of the NDA.
- Late Submissions

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. Pfizer states that they intend to submit a complete application and therefore, there are no agreements for late submission of application components.
- A chemistry pre-submission meeting is scheduled for July 14, 2017. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

PREA REQUIREMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. As of **May 5, 2017**, the following submission types: **NDA**, **ANDA**, and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note

that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

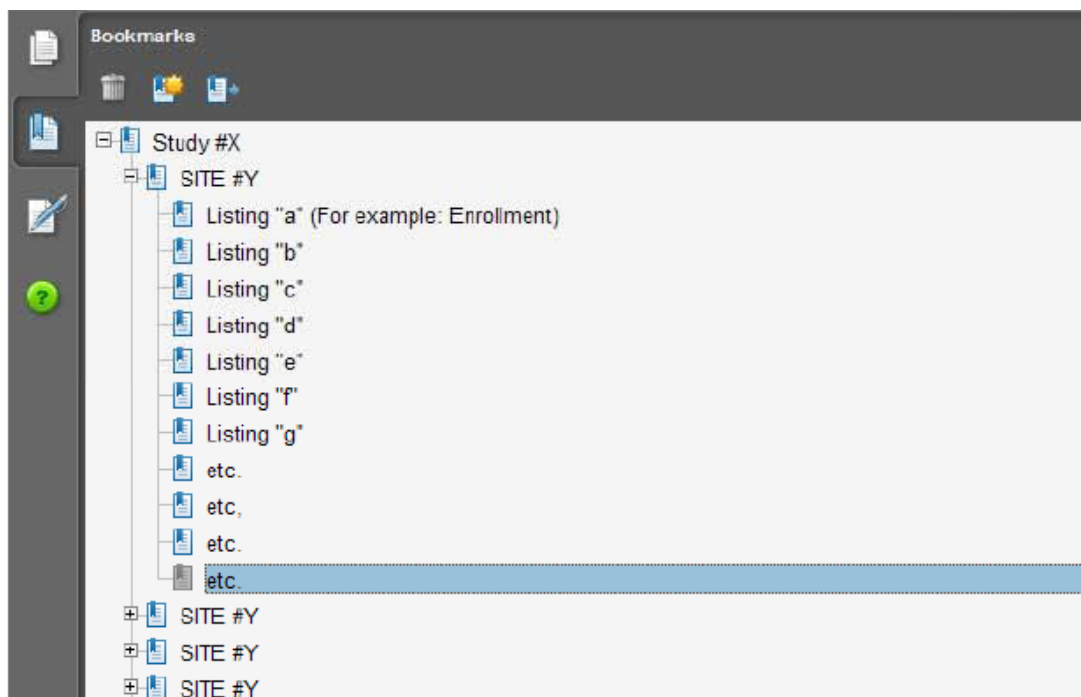
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

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

- c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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



III. Request for Site Level Dataset:

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

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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

DSI Pre-NDA Request Item¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

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



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

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

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

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

ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

ACTION ITEMS

No action items.

ATTACHMENTS AND HANDOUTS

July 26, 2013 Type C Briefing Document and August 19, 2013 Written Responses Only, in reference to Pfizer Response to Question 5.



i72775 Written
Responses_Final.pdf



Briefing Package -
Type C Meeting.pdf

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/s/

IDARA UDOH
06/26/2017