CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214622Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 104187

MEETING MINUTES

QED Therapeutics, Inc.
Attention: Amanda Roodhouse
Senior Director, Regulatory Affairs
8000 Marina Boulevard, Suite 400
Brisbane CA 94005

Dear Ms. Roodhouse:

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

We also refer to the teleconference between representatives of your firm and the FDA on July 28, 2020. The purpose of the meeting was to discuss the format and content of the proposed NDA, particularly, acceptability of topline results from Study CBGJ398X2204 to support submission of the NDA, the overall Table of Contents for the proposed NDA, and the contents and timing of the proposed Safety Update.

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

If you have any questions, please call me at 240-402-6571 or email me at Christina.Leach@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Christina Leach, PharmD
Regulatory Health Project Manager
Division of Regulatory Operations-Oncologic Diseases for DO3
Office of Regulatory Operations
Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Tuesday July 28, 2020 10:30am to 12pm EST
Meeting Location: Teleconference

Application Number: IND 104187
Product Name: Infigratinib (BGJ398, BBP-831, infigratinib phosphate)

Indication: Treatment of adult patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements, as detected by an FDA approved test.

Sponsor Name: QED Therapeutics, Inc.
Regulatory Pathway: 505(b)(1) of the Food, Drug, and Cosmetics Act

Meeting Chair: Steven Lemery, MD, MHS
Meeting Recorder: Christina Leach, PharmD

FDA ATTENDEES

Steven Lemery, MD, MHS	Division Director (acting), Division of Oncology 3 (DO3)
'Lola Fashoyin-Aje, MD, MPH	Deputy Division Director (acting), DO3
Shan Pradhan, MD	Clinical Reviewer, DO3
Sandra Casak, MD	Clinical Team Lead, DO3
Denali Kufrin, PhD	Nonclinical Reviewer, Division of Hematology, Oncology, Toxicology (DHOT)
Matthew Thompson, PhD, MPH	Nonclinical Team Lead, DHOT
Safaa Burns	Clinical Pharmacology Reviewer
Jeanne Fourie Zirkelbach, PhD	Clinical Pharmacology Team Lead
Abhishek Bhattacharjee	Biometrics Reviewer
Joyce Cheng	Biometrics Team Lead
Ashleigh Lowery	Division of Medication Error Prevention and Analysis (DMEPA) Team Lead
Dun Liang	CDRH Reviewer
Xing Wang	Product Quality Team Lead
Gerlie Gieser, Ph.D.	Biopharmaceutics Reviewer

Banu Zolnik, Ph.D.	Biopharmaceutics Team Lead
Rosane Charlab Orbach	Genomics
Christina Leach, PharmD	Regulatory Project Manager, DO3
Norma Griffin	Chief Project Management Staff, DO3

SPONSOR ATTENDEES

Name	Discipline	Title
Susan Moran, MD, MSCE	Clinical Development	Chief Medical Officer, QED
Stacie Shepherd, MD, PhD	Clinical Development	Senior Vice President, QED
Roo Vold, MD	Pharmacovigilance	Vice President, QED
David Martin, PhD	Nonclinical and Clinical Pharmacology	Vice President, QED
Miki Yamamoto, PhD	Regulatory Affairs	Vice President, QED
Mehrak Kiankarimi, PhD	Project Management	Vice President, QED
Amit Pande, MD	Clinical Development	Executive Director, QED
Amanda Roodhouse	Regulatory Affairs	Senior Director, QED
Ai Li, PhD	Biostatistics and Data Management	Senior Director, QED
Maribel Reyes, PhD	Clinical Pharmacology	Senior Director, QED
Harris Soifer, PhD	Translational Medicine	Senior Director, QED
Michael LeBlanc	Analytical Development	Director, QED

BACKGROUND

Regulatory

On September 3, 2009, Novartis Pharmaceuticals Corporation submitted investigational new drug (IND) application IND 104187 for the development of BGJ398 (infigratinib) for the treatment of advanced solid tumors.

On August 20, 2018, sponsorship of IND 104187 was transferred from Novartis Pharmaceuticals Corporation to QED Therapeutics, Inc. (QED).

On December 10, 2018, a Type C meeting was held to discuss QED's plans regarding registration of infigratinib for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or translocations (b) (4) based on results from Study CBGJ398X2204 (also referred to as Study 2204). FDA stated:

- "FDA will consider filing an application seeking the proposed indication based upon the efficacy endpoint of confirmed overall response rate (ORR) according to RECIST 1.1 per blinded independent radiology assessment if the ORR is large enough to be clinically meaningful and accompanied by sufficient durability and a

favorable benefit:risk profile such that the drug provides a benefit over available therapy."

- "Given the modest response rate observed to date, FDA requests that all responding patients be followed for a minimum of six months following onset of response (or until disease progression or discontinuation of treatment, whichever occurs first) in order to fully characterize duration of response."

On July 12, 2019, QED submitted a Fast Track Designation (FTD) request for infigratinib for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or translocations (b) (4) . On September 10, 2019, FDA granted FTD for infigratinib for "the first-line treatment of adult patients with unresectable locally advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or translocations to demonstrate a statistically significant improvement in overall survival or at least a 6-month improvement in median progression-free survival according to Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1 as assessed by a blinded independent radiology committee from a mature analysis, for patients randomized to receive infigratinib compared to those randomized to receive cisplatin and gemcitabine."

On May 24, 2019, QED submitted a meeting request to obtain advice regarding the analysis strategy for the Integrated Summary of Safety, the planned content of the Clinical Summaries of Effectiveness (SCE) and Safety (SCS), and the proposed format (CDISC) for datasets to be included in a planned NDA for infigratinib for the proposed indication "treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions or translocations (b) (4) ," based on the results of Cohort 1 of Study CBGJ398X2204, entitled "A Phase 2 Multicenter, Single Arm Study of Oral BGJ398 in Adult Patients with Advanced or Metastatic Cholangiocarcinoma with FGFR2 Gene Fusions or Other FGFR Genetic Alterations who Failed or are Intolerant to Platinum-Based Chemotherapy." FDA issued written responses August 7, 2019, which included the following:

- "FDA does not agree with QED's proposal to submit an NDA supported by data from Cohort 1 of Study 2204 based on an interim analysis conducted when the (b) (4) . FDA notes that this interim analysis was added in Amendment 4 to the Study 2204 protocol following prior evaluation of accumulated study data."

- "FDA is concerned that data from (b) (4) will not provide sufficient information to adequately characterize the response rate to infigratinib."

- "QED should include vascular/intravascular calcification or mineralization as an AESI."

- "A future NDA should also provide detailed information including a narrative for each patient who experienced an AE at least possibly related to vascular/intravascular mineralization or calcification based on the search strategy to be described in the ISS for these events."

On September 11, 2019, FDA granted orphan drug designation for infigratinib for the treatment of cholangiocarcinoma.

On October 16, 2019, as a follow-up to the August 7, 2019, written responses from FDA, QED submitted a meeting request to obtain feedback on additional information regarding pooling of safety and efficacy data across formulations, the proposed primary efficacy analysis to support an NDA, narratives to be included in the NDA, and assessments of important safety outcomes. The meeting was held as a Type C teleconference on December 20, 2019. FDA stated:

- "As stated in the protocol, the primary efficacy analysis set should consist of data from the first 106 patients with FGFR2 gene fusion / translocation-positive cholangiocarcinoma enrolled in Study CBGJ398X2204 who received at least one dose of infigratinib."

- "QED should present analyses based on the 106 patients dosed as the primary efficacy analyses at a pre-NDA meeting."

- That the original NDA should include data from the 106 patients that would support an approval determination.

- "FDA will consider efficacy analyses based on the first 92 patients to be sensitivity analyses."

FDA sent Preliminary Comments to QED on July 23, 2020.

SPONSOR QUESTIONS AND ANSWERS

1. Does the Agency agree that the topline results from Study CBGJ398X2204 show a favorable benefit-risk profile for infigratinib, thus supporting an NDA submission for accelerated approval?

   FDA Response: Although Study CBGJ398X2204 may support an NDA submission for the proposed indication, FDA cautions against a premature submission, considering that 12 patients (11.1%) appear to have an unconfirmed response and there is limited duration of response data. Whether infigratinib provides a meaningful clinical effect and whether the risk-benefit profile is favorable will be determined during review of the NDA. FDA recommends that

QED discuss whether a later data cut-off may result in a better description of the clinical effects of infigratinib.

QED Response 7/25/20: QED acknowledges the Agency's response and that this will be a review issue. Of the 108 subjects included in the topline results, 107 (99.1%) subjects treated with infigratinib had Stage IV cancer at study enrollment with a total of 104 (96.3%) subjects who had either progressed on prior gemcitabine-based regimen or regimen subsequent to the gemcitabine-based regimen. Thus, these patients represent a refractory patient population who have few effective therapeutic options and no established standard of care. The BICR-assessed ORR was 23.1% (95% CI: 15.6, 32.2), including 1 CR, with 8/25 of responders (32%) having a DOR of ≥6 months. Notably, the 95% CI based on the binomial distribution (Clopper-Pearson exact method) excluded 15% as the lower bound of the CI, supporting robust antitumor activity for this single-agent, oral, targeted therapy.

To provide clarification of the anticipated further maturation of the data, 12 subjects were ongoing at the time of data cutoff (31 March 2020), and 6 subjects have since discontinued study treatment. Of the 6 subjects ongoing, 2 subjects with BICR confirmed objective response (partial response) are included in the summary of the topline data. The remaining 4 ongoing subjects have been on the study for more than a year with stable disease per BICR. Given their duration on study, these patients are unlikely to have an initiation of objective response. Based on this we do not expect the overall response rate and median duration of response to notably change with additional follow-up.

The topline results provided in the briefing documents, and the planned submission will include a planned sensitivity analysis to further support the potential impact of ongoing patients. The Sensitivity Analysis Set includes subjects from Cohort 1 with FGFR2 fusion/translocation who had received at least one dose of infigratinib and have been followed for at least 10 months since start of study treatment. The 10-month period from the start of study treatment was designed to include approximately 4 months for time to objective response (assuming 2 scans at 8-week intervals, such that initial response is confirmed) and at least 6 months of follow-up until discontinuation for responders (median time to objective response is 3.6 months). The sensitivity analysis included 100 out of the total 108 subjects in the Interim analysis set 2. Overall, the results for primary and secondary efficacy endpoints were similar in the Sensitivity Analysis Set compared with the Interim Analysis Set 2 for Cohort 1.

Discussion during 7/28/20 t-con: FDA stated that ultimately the decision regarding timing of the submission would be QED's; however, FDA acknowledges based on QEDs response, that it is unlikely that further follow-up will notably change the results for ORR or DOR or the risk/benefit profile for infigratinib.

FDA recommended providing updated information from the subgroup of patients who are unconfirmed responders (who would now be considered non-responders) in the NDA, including the Assessment Aid. QED acknowledged.

2. Does the Agency agree with the proposed indication statement?

FDA Response: FDA does not object to the submission of a planned NDA with the proposed indication statement, however, the indication will be determined during review of the NDA.

QED Response 7/25/20: QED acknowledges the Agency's response and has no further comment.

Discussion during 7/28/20 t-con: No discussion occurred.

3. Does the Agency agree that the criteria have been met to justify Priority Review of this NDA?

FDA Response: Whether criteria for Priority Review have been met will be determined after submission of the NDA.

QED Response 7/25/20: QED acknowledges the Agency's response and has no further comment.

Discussion during 7/28/20 t-con: No discussion occurred.

4. Does the Agency agree with QED's proposal for a randomized trial demonstrating improvement of progression-free survival or overall survival in patients with unresectable locally advanced or metastatic cholangiocarcinoma with an FGFR2 gene fusion or rearrangement to serve as a confirmatory study if accelerated approval is granted?

FDA Response: FDA does not object to QED's proposal to conduct a randomized trial assessing progression-free survival or overall survival in patients with an FGFR2 gene fusion or rearrangement to serve as a confirmatory trial if accelerated approval is granted. Alternatively, QED may participate with other sponsors in conducting a clinical trial with different drugs being compared to a common control arm.

QED Response 7/25/20: QED is committed to completing a confirmatory trial in the most expeditious manner. Given the challenges of enrolling a rare population with high unmet need amidst a landscape of competitive trials, QED is exploring innovative ways to ensure completion of a confirmatory study a timely manner,

such as through collaboration with other sponsors. Feedback will be requested from the Agency once a protocol is available.

In line with exploration of innovative approaches, QED is considering other ways to optimize the ongoing study, including (b) (4). QED requests discussion of possible innovative approaches, and the Agency's input on whether there is a mechanism to obtain expedited feedback on clinical trial modifications of studies to confirm results under accelerated approval.

Discussion during 7/28/20 t-con: FDA acknowledged QED's response and will consider specific proposals at the time of submission to the Agency. One such proposal was to (b) (4)

FDA recommended a separate interaction (e.g., meeting or WRO or information request) to assess these potential changes to the protocol.

FDA also encouraged QED to enroll a patient population that would reflect the demographic characteristics of patients in the US.

5. Does the Agency agree that the proposed contents of the NDA as outlined in the Table of Contents of a complete NDA to support review?

FDA Response: FDA does not object to the proposed Table of Contents for the planned NDA.

QED Response 7/25/20: QED acknowledges the Agency's response and has no further comment.

Discussion during 7/28/20 t-con: No discussion occurred.

6. QED considers the safety and tolerability of infigratinib to be well defined and considers that routine pharmacovigilance and labeling will be sufficient to mitigate risks and preserve benefit, and therefore a Risk Management Plan or REMS is not needed. Does the Agency agree?

FDA Response: FDA agrees that a risk management plan or REMS is unlikely to be needed, but a final determination will be made during review of the NDA.

QED Response 7/25/20: QED acknowledges the Agency's response. QED is planning for production of packaging and labels and, given the challenges of the COVID-19 health crisis, is working to mitigate any potential delays in this process.

To help best mitigate these risks, would the Agency be able to provide preliminary feedback on the packaging (draft packaging provided in the pre-NDA briefing document in Appendix 8), and/or advise on available mechanisms to obtain feedback on the final packaging before the NDA submission?

Discussion during 7/28/20 t-con: FDA stated that it is difficult to provide feedback regarding packaging prior to receipt of information in the NDA submission.

7. QED proposes to include financial disclosure information for only Study CBGJ398X2204. Does the Agency agree with this approach?

FDA Response: Yes, FDA agrees the proposal is acceptable.

QED Response 7/25/20: QED acknowledges the Agency's response and has no further comment.

Discussion during 7/28/20 t-con: No discussion occurred.

8. Does the Agency agree that the two major infigratinib active metabolites (BHS697 and CQM157) have been sufficiently characterized by the studies conducted and proposed to be included in this NDA?

FDA Response: The characterization of the active metabolites appears sufficient to support the NDA. A final determination on the adequacy of the metabolite data will be a review issue.

QED Response 7/25/20: QED acknowledges the Agency's response and has no further comment.

Discussion during 7/28/20 t-con: No discussion occurred.

9. Does the Agency agree with QED's proposal for the 90-Day Update?

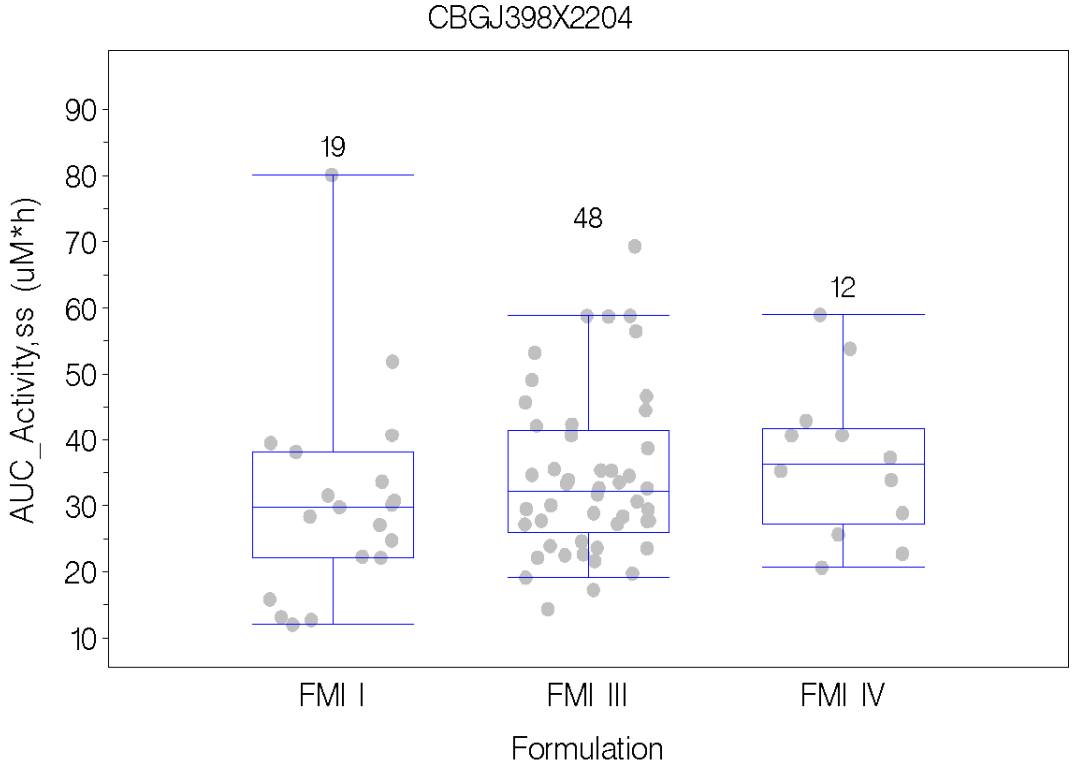
FDA Response: Adequate intensive PK data from Study GBGJ398X2204 to bridge the switch in formulation from FMI III to FMI IV should be submitted at the initial NDA submission to allow for adequate review. Clarify what portion of the 20 patient dense PK sampling from Study GBGJ398X2204 will be submitted at the time of the initial NDA for formulation FMI III and FMI IV.

QED Response 7/25/20: QED acknowledges the Agency's response and requests discussion to follow alignment on Question 1. Study CBGJ398X2204 collected intensive PK data in 20 patients administered FMI III in Cohort 1, and sparse PK data from 6 patients who received FMI IV in Cohort 1 (no intensive PK

data is available from this Cohort). This data will be provided in the NDA, in addition to intensive PK data from 3 patients in Cohorts 2 and 3.

FMI IV is a minor modification of FMI III with the only difference being [redacted] (b) (4) to improve manufacturability [redacted] (b) (4) This change is expected to be inconsequential and comparison of formulations (CSF, FMI I, FMI III, and FMI IV) across healthy volunteer studies showed non-significant differences in PK (AUC, C_{max}, T_{max}) across formulations. In addition, population PK analysis investigated formulation (CSF, FMI I, FMI III, and FMI IV) as a covariate, as previously indicated in the Type C Meeting held 20 Dec 2019. The model was further optimized and updated with additional CBGJ398X2204 FMI IV data as indicated in Section 4.8 of the pre-NDA briefing document. Consistent with the data provided for the December 2019 Type C meeting, no clinically meaningful differences in terms of exposure between the investigated formulations could be identified. In particular, formulation was tested in the systematic covariate search and did not meet the inclusion criteria for significant covariate effects, and the observed relative differences in AUC_{0-24} of the 3 analytes (infigratinib, BHS697, and CQM157) and $AUC_{activity}$ between subjects who received different formulations were minor (Figure 1).

Figure 1: Infigratinib Predicted $AUC_{activity}$ at Steady State by Formulation in CBGJ398X2204 (Population PK Analysis set)



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
The number of patients is above each box.

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Abbreviations: $AUC_{activity}$, combined exposure measure; AUC_Activity,ss, combined exposure measure at steady state; FMI I, final market image version 1; FMI III, final market image version 3; FMI IV, final market image version 4.
Source: d4pk\graphs\pnghi\eda\rpt-s2204-b-aucactss-form.png and rpt-s2204-b-aucact-form.png

In the initial NDA submission, intensive PK data will include the following:

- Cycle 1 Day 1: 20 patients on FMI III and 3 patients on FMI IV
- Cycle 1 Day 15: 12 patients on FMI III, and 1 patient on FMI IV.

Additionally, intensive PK data from FMI IV in healthy volunteers (N=20) and the assessment of the impact of formulation on infigratinib PK via Population PK modeling will be provided. Intensive PK data with FMI IV continues to be collected in newly enrolled cholangiocarcinoma patients (Cohorts 2 and 3) and while limited, may be provided with the 90-Day Update.

Discussion during 7/28/20 t-con: FDA stated that typically the pop PK approach is not used to assess for differences in formulation and that it is

important to have adequate data that would support the bridge between differences in formulation in the original NDA submission. FDA stated that the Agency will mostly rely on dense PK data that will be provided in the original application. As such FDA, stated that the proposal for the original NDA submission would be acceptable. FDA stated that a final determination of the adequacy of the data will be determined at the time of NDA review.

Regarding the information in the 90 day update, FDA did not object to the submission of limited additional PK data. FDA stated that it does not appear that the information in the 90 day update will be necessary to take an action on the application.

FDA stated that the proposal for the safety update and updated duration of response data was acceptable; however, FDA may not include the updated DOR information in product labeling.

10. QED has developed (b) (4)

FDA Response: The plan to submit a (b) (4) appears reasonable. The acceptability of the (b) (4) will be determined during the NDA review, (b) (4)

QED Response 7/25/20: QED acknowledges the Agency's response and that the Agency would be open to review (b) (4) during NDA review. Would the Agency agree to review (b) (4) before the original NDA submission, for earlier feedback?

(b) (4)

(b) (4)

Discussion during 7/28/20 t-con: FDA indicated that based on the information provided, it would not be feasible to make a final determination on the acceptability (b) (4) before original NDA submission. FDA explained that the evaluation of the (b) (4)

Post-NDA approval (b) (4) are beyond the scope of the current meeting. (b) (4)

ADDITIONAL COMMENTS:

Clinical

11. In addition to Forms 3454/3455 for financial certification and disclosure in Module 1.3.4, please submit the information in a spreadsheet (SAS transport file or xlxs file).

    QED Response 7/25/20: QED acknowledges the Agency's response and will provide an accompanying spreadsheet in the NDA.

    Discussion during 7/28/20 t-con: No discussion occurred.

12. Regarding QED's correspondence dated June 26, 2020, requesting participation in the Real Time Oncology Review (RTOR), FDA agrees that the application may be submitted under the RTOR program. However, FDA and QED should further discuss the components of the submission considering FDA's response to Question 1 above.

    QED Response 7/25/20: QED acknowledges the Agency's response and requests discussion to follow alignment on Question 1.

    Discussion during 7/28/20 t-con: FDA did not object to the submission of the NDA under the RTOR program with the proposed timelines considering the discussion under Question 1.

    FDA asked about whether QED would be interested in participating in Project Orbis. QED stated they would potentially be interested. FDA recommended confirming interest as soon as possible so that FDA can reach out to the other countries to determine their interest.

CDRH

13. Provide the pre-specified definition for eligible FGFR2 alterations. At this time, CDRH recommends that QED adopt the existing definition for the companion diagnostic. Indicate whether the protocol's definition for the variants was consistently applied across the different testing sites, specimen types (tumor vs ctDNA), and the local tests. The definition used to define the intent-to-treat population should generally be aligned with the CDx test.

    QED Response 7/25/20: QED acknowledges the Agency's comment. The pre-specified protocol definition of eligible FGFR2 alterations in the primary analysis set is "FGFR2 gene fusions/translocations." The word "translocation" was intended as a general word for FGFR2 rearrangements based on the terminology used for structural variants when the protocol was initiated in 2014. The pre-

specified protocol definition for “FGFR2 gene fusions/translocations” was consistently applied across testing laboratories, specimen types, and local tests. QED has adopted the existing definition for “FGFR2 fusions and select rearrangements” for F1CDx (P170019/S013). This definition will be used to evaluate clinical efficacy in the bridging study to ensure the F1CDx-intent-to-treat population corelates with patient responses. No further discussion is requested.

Discussion during 7/28/20 t-con: No discussion occurred.

14. In the NDA submission, please include the following patient-level data (xpt file format) for Study CBGJ398X2204 (Cohort 1): patient ID, specimen type, local test method, local test result and interpretation, clinical trial assay (CTA) result and interpretation, and F1CDx test result (e.g., FGFR2-BICC1) and interpretation (e.g., fusions from the non-fusion rearrangements). Provide the definitions for fusion vs non-fusion rearrangement used by the CTA and F1CDx and an explanation for all analytical and/or interpretation discordance in assignment of fusions vs non-fusion rearrangements. This information would preferably be submitted in a separate dataset. In addition, submit assay reports if available.

QED Response 7/25/20: QED acknowledges the Agency’s comment and will provide the following patient-level data for CBGJ398X2204 (Cohort 1): patient ID, specimen type, local test method, local test result and interpretation, clinical trial assay (CTA) result and interpretation, definitions for fusion vs non-fusion rearrangement used by the CTA and the CTA assay reports, if available.

QED requests to cross reference the Foundation Medicine sPMA of the companion diagnostic F1CDx (see (b) (4)) for CBGJ398X2204 F1CDx results, interpretation (e.g., fusions from the non-fusion rearrangements), and explanation for all analytical and/or interpretation discordance in assignment of fusions vs non-fusion rearrangements as this data may not be available at the time of NDA submission. Does the Agency agree with this request?

Discussion during 7/28/20 t-con: FDA stated that it will be helpful to have the specific definitions used for both the local assays and the FMA assay in the

NDA submission. FDA asked that QED submit the FM data and information to the NDA, but agreed that because this would be a minor component not necessary to act on the NDA, it could be submitted in October.

15. To the extent possible, please ensure the data submitted to the NDA is aligned with the data submitted to CDRH by the sponsor of the companion diagnostic.

QED Response 7/25/20: QED acknowledges the Agency’s comment and is working closely with Foundation Medicine to ensure the data submitted to the

NDA is aligned with the data submitted to CDRH by the sponsor of the companion diagnostic. No further discussion is requested.

Discussion during 7/28/20 t-con: No discussion occurred.

16. Patients were enrolled into Study CBGJ398X2204 based on testing using a variety of local tests including the Foundation MedicineOne (F1CDx) test. Please plan to provide information regarding the genetic variations and the detailed criteria on the basis of which patients were screened/enrolled in the trial and clarify whether these criteria align with the current FDA-approved F1CDx device.

QED Response 7/25/20: QED acknowledges the Agency's comment and will provide patient-level information on the local test result and interpretation of the FGFR2 genetic variation that was used as the basis for screening/enrollment. These criteria were intended to align with the current F1CDx device for "FGFR2 fusions and select rearrangements" (P170019/S013). No further discussion is requested.

Discussion during 7/28/20 t-con: No discussion occurred.

17. It appears for the confirmatory study QBGJ398-301, QED will continue to plan to use Foundation Medicine and other local laboratories to screen patients for eligibility. QED should plan to bank available test positive and a random subset of test negative samples to support a bridging study as needed. Collect the following information, as available, from each testing site that forwarded eligible patients to the trial:

    a. Local test reports with all information captured (e.g., where the test was performed, the test methodology, the specimen type, minimal data on the analytical performance of the test, test name, etc.) in the Case Report Forms Test method (e.g., NGS, PCR), instrument, size of the panel;

    b. Description of the test limit of detection for fusions specifically;

    c. Description of the specific biomarkers evaluated (e.g., FGFR-BICC1 etc.) and the prevalence.

QED Response 7/25/20: QED acknowledges the Agency's comment and agrees to bank additional samples to support a bridging study and will collect the test information for subjects who enroll using a local laboratory. No further discussion is requested.

Discussion during 7/28/20 t-con: No discussion occurred.

Clinical pharmacology

18. FDA recommends the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (available at https://go.usa.gov/xn4qB).

    QED Response 7/25/20: QED acknowledges the Agency's recommendation and will follow the FDA guidance "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" in the labeling to be submitted in the NDA. No further discussion is requested.

    Discussion during 7/28/20 t-con: No discussion occurred.

Address the following questions in the Summary of Clinical Pharmacology:

19. What are the bases for selecting the doses and dosing regimens 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 dose and administration.

    QED Response 7/25/20: QED acknowledges the Agency's question and will provide a detailed assessment of the bases for the dose and dose regimen used in the trials intended to support the NDA.

    The dose and dosing regimen of 125 mg 3 weeks on/1 week off in the trial (CBGJ398X2204) intended to support the marketing application is based on the identified recommended Phase 2 dose in the dose escalation study CBGJ398X2101. This study assessed PK, safety, and antitumor activity of infigratinib in patients with advanced solid malignancies at doses ranging from 5 mg QD to 150 mg QD.

    A starting dose of 125 mg/day provides all patients the opportunity to quickly achieve an efficacious dose, while the biomarker of hyperphosphatemia, a class effect of FGFR inhibitors, provides for a readily measurable indicator for individual dose titration.

    The initial NDA will also include assessment of the appropriateness of the proposed dose regimen for study CBGJ398X2204 by providing exposure-response modeling and simulations for efficacy and safety. In this analysis, dose reductions in the study will be taken into consideration. Finally, the exposure-response simulations will provide alternate dose levels to confirm that 125 mg 3 weeks on/1 week maximizes probability of response while not significantly increasing the probability of adverse events relative to lower doses.

Individuals who required dose modifications will be identified in the NDA and time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration will also be provided. QED welcomes further discussion during the meeting.

Discussion during 7/28/20 t-con: FDA stated that the proposed E-R analyses appear acceptable as a justification for the dose. FDA will review this data and a final determination will be made at the time of the review.

20. What are the exposure-response relationships for efficacy, safety, and biomarkers?

QED Response 7/25/20: QED acknowledges the Agency's question and will provide exposure-efficacy and exposure-safety analysis results for CBGJ398X2204 in the initial NDA. No further discussion is requested.

Discussion during 7/28/20 t-con: No discussion occurred.

21. What is the effect of the drug on the QT/QTc interval?

QED Response 7/25/20: QED acknowledges the Agency's question and will provide in the initial NDA, in lieu of a dedicated thorough QT/QTc study, assessment of QT/QTc interval effects based on PK/ECG data from the dose escalation study, CBGJ398X2101, and the CBGJ398X2204 study, as outlined in the cardiac safety plan submitted to IND 104,187 on 06 July 2020 as Ser. No. 0357. In these studies, time-matched PK and 12-lead ECG data were collected. Subsequently, a PK-QTc linear mixed-effect modeling approach was used to examine the relationship between the change from baseline QTc interval and the plasma concentration of infigratinib and its major metabolites. The preliminary analysis shows that there is no significant increase in QTc detected at the observed steady state maximum concentration observed in CBGJ398X2204. No further discussion is requested.

Discussion during 7/28/20 t-con: No discussion occurred.

22. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?

QED Response 7/25/20: QED acknowledges the Agency's question and will provide the characteristics of absorption, distribution, and elimination (metabolism and excretion) in the NDA. No further discussion is requested.

Discussion during 7/28/20 t-con: No discussion occurred.

23. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendations with regard to meals or meal types.

QED Response 7/25/20: QED acknowledges the Agency's question and has investigated the effects of food on the bioavailability of infigratinib (FMI I and FMI III formulations). Food increased the exposure of infigratinib (1.7 to 2.2-fold); therefore, it is recommended that infigratinib is taken 1 hour before or 2 hours after a meal, consistent with administration in Study CBGJ398X2204.
The food effects on the bioavailability of infigratinib (FMI IV) were not investigated. Given the lack of significant difference in exposure of infigratinib between formulations, QED does not plan to conduct a food effect study with FMI IV.

Does the Agency agree that this current clinical pharmacology package is adequate to support the dose recommendations with regard to food effect?

Discussion during 7/28/20 t-con: No discussion occurred.

24. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunction) influence exposure, efficacy, or safety? What dose modifications are recommended?

QED Response 7/25/20: QED acknowledges the Agency's question and will provide detailed results of the extrinsic and intrinsic factor and their influence on infigratinib exposure in the NDA. A series of drug-drug interaction clinical studies have been carried out to characterize the drug interaction potential of infigratinib (please see Section 5.3.2.2 of the TOC provided in Appendix 1 of the briefing document). Strong CYP3A4 inhibitors increased infigratinib plasma concentration, and strong CYP3A4 inducers decreased infigratinib plasma concentration; the recommendation will be to avoid coadministration with strong CYP3A4 inhibitors or inducers. The proton pump inhibitor lansoprazole decreased infigratinib plasma concentration; the recommendation will be that proton pump inhibitors should be avoided (b) (4) . Infigratinib should be taken ≥2 hours before or 10 hours after dosing with H2RA. Antacids may be taken 2 hours before infigratinib dosing. These recommendations are consistent with infigratinib administration in CBGJ398X2204.

The effect of intrinsic factors such as sex, race, disease, etc., on infigratinib exposure are being evaluated via Population PK modeling (5.3.3.5; QED-PMX-001) and on exposure-response modeling (5.3.4.2; QED-PMX-002). The population PK model did not identify sex, race, age, BMI, or body weight as a significant covariate on infigratinib PK; therefore, no dose adjustment is recommended based on these intrinsic factors.

Finally, a hepatic impairment study (5.3.3.3; QBGJ398-107) has been conducted in mild and moderate hepatic impairment subjects and healthy volunteers. The effect of liver function (NCI criteria) was also assessed in the Population PK model. QED is proposing a dose of 75 mg 3 weeks on/1 week off in moderate (Child-Pugh B) hepatic impairment patients since the mean plasma exposure of infigratinib increased more than 2-fold in the dedicated hepatic impairment study. QED proposes (b) (4) for patients with mild (Child-Pugh A or NCI B1/B2) hepatic impairment (b) (4) dose adjustment in patients with mild hepatic impairment. QED welcomes further feedback from the Agency.

Discussion during 7/28/20 t-con: No discussion occurred.

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

25. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

    QED Response 7/25/20: QED acknowledges the Agency's recommendation and will provide the requested information in the NDA. No further discussion is requested.

    Discussion during 7/28/20 t-con: No discussion occurred.

26. Provide a final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.

    QED Response 7/25/20: QED acknowledges the Agency's recommendation and will provide the requested information in the NDA. No further discussion is requested.

    Discussion during 7/28/20 t-con: No discussion occurred.

27. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The patients' unique ID numbers in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.

- 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 patients that have been excluded from the analysis should be flagged and maintained in the datasets.

- Identify individual patients with dose modifications; the time to the first dose reduction, interruption or discontinuation; and the reasons for dose modifications in the datasets.

QED Response 7/25/20: QED acknowledges the Agency's recommendation and will provide the requested information in the NDA. No further discussion is requested.

Discussion during 7/28/20 t-con: No discussion occurred.

28. Submit the following for the population pharmacokinetic analysis reports:

- Standard model diagnostic plots.

- Individual plots for a representative number of patients. Each individual plot should include observed concentrations, the individual prediction line, and the population prediction line.

- Model parameter names and units in tables.

- Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

QED Response 7/25/20: QED acknowledges the Agency's recommendation and will provide the requested information in the NDA. No further discussion is requested.

Discussion during 7/28/20 t-con: No discussion occurred.

29. Submit the following information and data to support the population pharmacokinetic analysis:

- SAS transport files (*.xpt) for all datasets used for model development and validation.

- A description of each data item provided in a Define.pdf file. Any concentrations or patients that have been excluded from the analysis should be flagged and maintained in the datasets.

- Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

QED Response 7/25/20: QED acknowledges the Agency's recommendation and will provide the requested information in the NDA. No further discussion is requested.

Discussion during 7/28/20 t-con: No discussion occurred.

30. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at

- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK,

- http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and

- http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometric data and models submission guidelines.

QED Response 7/25/20: QED acknowledges the Agency's recommendation and will provide the requested information in the NDA. No further discussion is requested.

Discussion during 7/28/20 t-con: No discussion occurred.

31. Include the following items when QED submits the QT study report:

    a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed

    b. Electronic copy of the study report

    c. Electronic or hard copy of the clinical protocol

    d. Electronic or hard copy of the Investigator's Brochure

e. Annotated CRF

f. A data definition file which describes the contents of the electronic data sets

g. 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

h. 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 the 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)

i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point

j. Narrative summaries and case report forms for any:
   i. Deaths (cardiovascular / arrhythmogenic)
   ii. Serious adverse events (cardiovascular / arrhythmogenic)
   iii. Episodes of ventricular tachycardia or fibrillation
   iv. Episodes of syncope
   v. Episodes of seizure
   vi. Adverse events (cardiovascular / arrhythmogenic) resulting in the subject discontinuing from the study

k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

l. A completed Highlights of Clinical Pharmacology Table Advancing in this field – and possibly reducing the burden of conducting QTstudies – depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making the data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at http://cardiac-safety.org/ecg-database/.

QED Response 7/25/20: QED acknowledges the Agency's recommendation and plans to provide the requested information in the NDA, according to the cardiac safety plan submitted to IND 104,187 on 06 July 2020 as Ser. No. 0357. Please see also QED's response to FDA Comment #21.

QED would like to ask for clarification for Item j (i-vi) Narrative summaries and case report forms. Could the Agency please clarify if this request applies to cases limited to and within the final QT study report (2 studies), or if the request should also encompass the broader ISS dataset? Please also clarify if narrative summaries/case report forms should be provided for both non-serious and serious events of syncope, seizure, ventricular tachycardia, ventricular fibrillation (if there are any).

Discussion during 7/28/20 t-con: FDA will provide a detailed response following this meeting.

Post meeting response: The request for "narratives and case report forms" applies to the broader ISS dataset. It applies to both non-serious and serious events of syncope, seizure, ventricular tachycardia, and ventricular fibrillation (if there are any). Refer to the "QT Evaluation Report Submission Checklist" located at the IRT website (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt) for details.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our June 4, 2020, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that it is unlikely that a REMS, or other risk management program would be necessary, but a final determination will be made during the review of the NDA.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

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[4] and Pregnancy and Lactation Labeling Final Rule[5] 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.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information 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*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* 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 ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

ISSUES REQUIRING FURTHER DISCUSSION

- None

ACTION ITEMS

- None

ATTACHMENTS AND HANDOUTS

[6] https://www.fda.gov/media/84223/download
[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[8] https://www.fda.gov/media/85061/download

- QED Therapeutics, Inc. responses to preliminary comments received July 25, 2020.

21 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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