CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761212Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 131463

MEETING PRELIMINARY COMMENTS

Lupin Limited
Attention: Debashis Mohanty
US Agent
111 South Calvert St., 24th Floor
Harborplace Tower
Baltimore, MD 21202

Dear Mr. Mohanty:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LUBT 004.

We also refer to your correspondence dated and received September 30, 2020, requesting a meeting to discuss the content and format of the planned 351(k) BLA for LUBT 004.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at 301-796-7775.

Sincerely,

{See appended electronic signature page}

May Zuwannin
Regulatory Project Manager
Nonmalignant Hematology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Biosimilar
Meeting Category: BPD Type 4

Meeting Date and Time: November 12, 2020, 9-10 AM (ET)
Meeting Location: Teleconference

Application Number: IND 131463
Product Name: LUBT 004
Indication: LUBT004 is being developed for the same indications as approved for US-licensed Neulasta
Sponsor Name: Lupin Pharmaceutical, Inc.
Regulatory Pathway: 351(k) of the Public Health Service Act

FDA ATTENDEES (tentative)

OCHEN, Division of Nonmalignant Hematology (DNH)
Ann Farrell, MD, Director
Albert Deisseroth, MD, PhD, Supervisory Associate Director
Kathy Robie-Suh, MD, PhD, Clinical Team Lead
Hyon-Zu Lee, PharmD, Clinical Reviewer

OCHEN, Division of Pharm/Tox (DPT)
Todd Bourcier, PhD, Nonclinical Team Lead (Acting)
Pedro Del Valle, PhD, ATS, Nonclinical Reviewer

Office of Biostatistics (OB), Division of Biometrics IX
Yeh-Fong Chen, PhD, Statistical Team Lead
Sarabdeep Singh, PhD, Statistical Reviewer

Office of Clinical Pharmacology (OCP)
Sudharshan Hariharan, PhD, Clinical Pharmacology Team Leader
Anusha Ande, PhD, Clinical Pharmacology Reviewer

Office of Regulatory Operations (ORO)
Charlene Wheeler, MSHS, Chief, Project Management Staff (Acting)
May Zuwannin, Regulatory Project Manager

Office of Biotechnology Products (OBP)
Zhenzhen Liu, PhD, Quality Review Team Lead
Tracy Denison, PhD, Quality Reviewer
Susan Kirshner, PhD, Review Chief
Marlene Schultz-DePalo, M.S., M.A., RAC, OBP Biosimilar Program and Policy Analyst

Joel Welch, PhD, Review Chief

Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis (DMEPA)
Hina Mehta, PharmD, Team Leader
Stephanie DeGraw, PharmD, Safety Evaluator

Office of Therapeutic Biologics and Biosimilars (OTBB)
Stacey Ricci, MEng, ScD, Acting Director Scientific Review Staff
Sarah Schrieber, Pharm.D., Scientific Reviewer
Cristina Ausin, Ph.D., Scientific Reviewer
Sarah Brown, Policy Analyst
Tyree Newman, Senior Regulatory Health Project Manager
Alison Falb, J.D., Regulatory Counsel

SPONSOR ATTENDEES

Cyrus Karkaria	President, Lupin Limited (Biotech Division)
Kalpana Vanam	Senior VP Regulatory Affairs
Akshaya S. Odak	Head, Regulatory (Biotech)
Sanjay Tiwari	Director R & D
Richard Peck	VP Regulatory Affairs
Chirag Shah	Director Clinical Research
Debashis Mohanty	Senior Manager Regulatory Affairs and US Agent

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 12, 2020, 9-10 AM, by teleconference between Lupin Pharmaceutical and the Division of Nonmalignant Hematology. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Lupin Pharmaceuticals Inc. is developing LUBT 004 as a proposed biosimilar to US-licensed Neulasta.

The purpose of this meeting is to discuss the content and format of the planned BLA. Specific objectives of the meeting are to discuss and seek the Agency's concurrence on the overall content of the sections and the placement of the data across the different modules of the proposed BLA

FDA may provide further clarifications of, or refinements and/or changes to these preliminary responses and the advice provided at the meeting based on further information provided by Lupin Pharmaceutical and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).

2.0 DISCUSSION

Question 1: Lupin plans to submit the 351(k) BLA for proposed biosimilar to US licensed Neulasta. The placement of data/report/information across the different modules of eCTD is provided in the Annex 1 -Table of contents. Does the proposed content and format of the 351(k) BLA for Lupin Pegfilgrastim as presented in 'Annex 1 -Table of Contents', meets the Agency's expectations for e-CTD submission?

FDA Response: The Agency prefers that information on manufacture of the critical intermediate, unpegylated LUBT 004 (CI), and LUBT 004 drug substance (DS) be provided in separate modules 3. Alternatively, you may provide the information on CI, and DS in completely separate file series under a single module 3. However, information on the CI and DS should not be commingled in Module 3 except where CI is used in the manufacture of DS, because it is difficult to track changes to the file when information is commingled. Summary information on the manufacture of the PEG critical reagent should be provided in the DS module under 3.2.S.2.3 Control of Materials.

Lupin's proposal for overall description of CMC information to go in each part of modules 2 and 3 is otherwise acceptable. Also, we have the comments below as well as additional CMC comments at the end of this document for you to consider when preparing your 351(k) submission:

- **Ensure your quality overall summaries in Module 2 provide a general introduction and overview for information provided in Module 3. For ease of review, it is recommended to include hyperlinks to referenced sections in Module 3.**

- **Ensure your narrative describing the comparative analytical assessment explains the protocol(s) followed. If the data are derived from multiple executed protocols, clarify which data come from which protocol and the overall rationale for how the protocols were designed and executed.**

- **Along with batch records, provide a table with links to different parts (e.g. process steps or unit operations) of the batch record(s). If feasible, batch records could be provided with searchable text to facilitate review.**

- **It is unclear whether you plan to provide information regarding shipping qualification of the CI and DS. If the CI is manufactured at different sites from DS, DS is manufactured at a different site from drug product (DP), or both, provide relevant shipping qualification data in your 351(k) BLA. See additional comments at the end for more advice regarding shipping qualification.**
- **Clearly indicate which facilities were involved in generating the comparative analytical assessment data provided to support a determination that LUBT 004 and US-licensed Neulasta are highly similar. These facilities may also be subject to a pre-licensing inspection to support your 351(k) submission.**

Question 2: Materials used in the manufacturing of the Lupin Pegfilgrastim, such as raw materials and excipients, will be listed in the eCTD section 3.2.S.2.3, identifying usage of each material in the manufacturing process. If the raw materials and excipients are of pharmacopoeial grade (USP and /or Ph. Eur./ JP/ BP), Lupin believes that the name of the vendor/s or supplier/s need not be defined in section 3.2.S.2.3. Does the Agency concur with our understanding?

FDA Response: Yes, we generally agree that materials conforming with United States Pharmacopeia (USP) compendial standards do not need to be specified by the vendor but you should indicate their compliance with the USP. Materials that only follow certain international standards, e.g. European Pharmacopeia or Japanese Pharmacopeia, may also be acceptable provided justifications for their suitability are provided. As part of GMPs, it is your responsibility to ensure all vendors or suppliers of raw materials are adequately qualified and verified to provide materials of the expected quality.

Question 3: In the 351(k) BLA submission, Lupin intends to include the information pertaining to evolution of release specification and analytical procedures for pegfilgrastim drug substance and drug product during the course of development, in eCTD section 3.2.S.2.6 and 3.2.P.2.3, respectively. Does the Agency concur with the company's approach?

FDA Response: It is acceptable to place the history of release specification and analytical procedures for DS and DP in eCTD section 3.2.S.2.6 and 3.2.P.2.3, respectively.

Question 4: Lupin Pegfilgrastim manufacturing process has (b) (4) . It is characterized by using a battery of orthogonal tests for its

physicochemical and functional aspects in a standalone manner. Lupin plans to place the data of (b) (4) characterization in the section 3.2.S.3.1, followed by Lupin Pegfilgrastim structural elucidation and other characteristics in the same section. Does agency concur with this data placement?

FDA Response: The Agency does not concur with your proposal, please refer to our response to Question 1 above, regarding module organization.

Question 5: The comparative analytical assessment results and conclusion of Lupin Pegfilgrastim and US licensed Neulasta will be provided in the section 3.2.R.3. Lupin plans to present the summary results and conclusions of the analytical assessment in the section whereas the detailed signed report shall be provided as an attachment. Does Agency concur with Lupin's plan?

FDA Response: This approach is acceptable. Ideally, supplemental reports included would be in pdf formats that include searchable text. Hyperlinks to the referenced supplemental reports are recommended to be provided in the summary of comparative analytical assessment section.

Question 6: At the time of the 351(k) BLA submission, Lupin proposes to submit 3 months of real time stability data at the recommended storage condition of 5°C ± 3°C for pegfilgrastim drug product process validation batches. Stability results of 6 months for pegfilgrastim drug product will be made available to the Agency during review of BLA. Does the Agency concur with the submission of 351(k) BLA with 3 months real-time stability data for drug product process validation batches and 6 months stability data to be submitted during the review period?

FDA Response: Per ICH Q5C, a minimum of 6 months stability data at the time of submission should be submitted in cases where storage periods greater than 6 months are requested. Your proposed stability data submission strategy may be acceptable depending on whether you can leverage data from developmental drug product batches. The dating period for LUBT 004 will be determined based on real time stability data. If you intend to use stability results using pre-process qualification DP then comparability of pre- and post-process qualification DP should be provided along with an assessment of the impact of manufacturing process changes to product quality. You may update the stability data within 8 months from the BLA submission date.

In order to support your proposed dating period for drug product, you may wish to provide a "simple stability update" which is defined as follows: Stability data and analyses performed under the same conditions and for the same drug product batches in the same container closure system(s) as described in the stability protocol provided in the original submission. This update will use the same tabular presentation as in the original submission as well as the same mathematical or statistical analysis methods (if any) and will not contain any

matrix or bracketing approaches which deviate from the stability protocol in the original BLA.

Question 7: Lupin has done a risk evaluation for the presence or potential for the formation of nitrosamine impurity during the manufacturing process of Lupin Pegfilgrastim. Lupin plans to place this risk assessment in the section 3.2.S.2.3 as an attachment to the section. Does the Agency concur with the plan?

FDA Response: In general, your plan may be acceptable. We recommend including in Section 3.2.S.2.3 a summary of the risk assessment approach and conclusions and refer to the attached internal report.

Question 8: During the initial development of pegfilgrastim, Lupin has conducted a battery of in-vivo non-clinical studies to meet the requirements of local health authority, DCG(I) (Drugs Controller General of India). As per the BPD Type 2 meeting minutes obtained on November 4, 2016, FDA has recommended us to follow, a risk-based approach for determining the necessity of animal studies to support the opening of an IND for a biosimilar development program. Subsequently, in the IND, in-vivo non-clinical studies were submitted which served the purpose as a "supporting information" only. Moving further, to obtain licensure of pegfilgrastim under section 351(k), a risk-based approach has been followed. Accordingly, Lupin plans to submit only in-vitro pharmacology data under section "4.2.1.1 Primary pharmacodynamics" and does not propose to submit in-vivo toxicological data under section 4.2.3 toxicology. Does the Agency concur with this proposal?

FDA Response: The Agency agrees with your approach. In your 351(k) BLA, provide your justification for why animal studies are unnecessary in your application under section 351(k)(2)(A)(ii) of the PHS Act.

Question 9: The clinical program for Lupin Pegfilgrastim includes two clinical studies, 1) "PK-PD with immunogenicity" in healthy subjects 2) "patient immunogenicity" study in breast cancer patients. Lupin plans to place clinical package in Module 5 in the following fashion.

A. CSR of "PK-PD with immunogenicity" study along with its appendices, the methods validation (MV) protocols & reports and sample analysis report for PK/PD parameters will be provided in section 5.3.4.1, as individual pdf files. While MV protocols and reports with sample analysis report for immunogenicity parameters will be placed in 5.3.5.3. The MV protocols and reports for PK, PD and immunogenicity parameters will be listed in section 5.3.1.4. and linked to respective sections, to ease review process.

B. The CSR of "patient immunogenicity" study with its appendices will be provided in section 5.3.5.1. The ADA Method validation protocols and reports will be

placed 5.3.5.3 but it will be listed in section 5.3.1.4 and will be linked for the ease review process.

C. Under section 5.3.5.3, for both studies ("PK-PD with immunogenicity" study and "patient Immunogenicity" study), the integrated summary of immunogenicity assessments including but not limited to, the followed assay format, positive control used, method validation summary and conclusion will be provided. Also, ADA method validation (MV) protocols, MV reports, sample analysis report and statistical evaluation will be provided, as attachments for both the studies.

D. Formal ISS and ISE are not planned. However, the efficacy and safety results of both the studies in the form of summaries will be provided within Module 2 (i.e., Modules 2.7.3 and 2.7.4, respectively).

Does agency agree with the above placement plans?

FDA Response: The proposal to provide the summaries of clinical safety and efficacy in the Module 2 (under section 2.7) and not including formal ISS and ISE is acceptable. However, in your briefing package, it states that in the "PK/PD study with immunogenicity", a total of 92 healthy adult male subjects are planned. Provide clarification whether healthy female subjects were also enrolled in the study. Also provide clarification if both the PK/PD study (ARL/18/360) and the immunogenicity study (LRP/PegGCSF/2016/004) were conducted in India. As communicated to you as post-meeting addendum of the October 5, 2016 meeting minutes, the Agency has questions regarding differences in population haplotypes between certain populations, as compared to the general U.S. population, and whether any differences could potentially impact the sensitivity of detecting differences in immune response, should they exist, or the observed magnitude of immune response. As such, you should provide a justification as to how the results of your comparative immunogenicity assessment in the population used in your studies support a demonstration of no clinically meaningful differences between your proposed product and US-licensed Neulasta as a part of supporting licensure of LUBT 004 in the US.

We have the following statistical comments for your consideration:

a. The Agency recommends evaluating safety of the drug before the sample size re-estimation. If there is no concern of safety, you may proceed to perform interim analysis for sample size re-estimation and at your own choice to increase the sample size or not.

b. For the analysis of the primary endpoint proportion of patients with cumulative incidence of anti-drug antibodies, please use the upper bound of 1-sided 90% interval with the prespecified margin, rather than 2-sided 95% confidence interval. Please amend your protocol

and SAP on the primary analysis and sample size calculation accordingly.

c. The Agency is concerned that the assumed incidence of anti-drug antibody rate of (b) (4) in the sample size calculation is too small and this may be overly optimistic assumption about the immunogenicity of LUBT 004 and US-licensed Neulasta.

Question 10: Under section "5.3.5.4 Other studies" Lupin plans to place human factors (HF) assessment package which will include justification for HF waiver along with threshold analysis and use error risk assessment. Does agency agree to the proposal of placing HF assessment package in the said section in the 351(k) BLA?

FDA Response: If you have previously submitted the threshold analysis, use error risk assessment, and justification for HF waiver then you can cross-reference the prior submission and include the eCTD sequence number and date of submission. You do not need to resubmit the electronic files when referencing that document.

Question 11: Under eCTD section 5.2, Lupin plans to provide 2 tables. In Table 1, study wise all details will be provided. In Table 2, information of "PK/PD with immunogenicity" study and "patient immunogenicity" study with regard to investigator details will be provided. Does the Agency concur with this plan?

FDA Response: The proposal is acceptable.

Question 12: As per the BPD Type 2 meeting minutes obtained on November 4, 2016, Lupin would like to submit the required information in the planned 351(k) BLA to seek extrapolation for orphan indication, "Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome)". In this context,

A. Does the Agency agree to the proposal of placing an "extrapolation of indication" under eCTD section "5.3.5.4 other studies" covering totality of evidence to demonstrate bio-similarity of Lupin pegfilgrastim to US licensed Neulasta?

B. Would FDA review Lupin's 351(k) BLA for both indications and tentatively grant us approval (licensure) for the orphan indication?

C. Lupin proposes to submit two pack inserts (PI), one without the orphan indication and other covering both indications, under Module 1. Does the Agency concur with the proposal?

FDA Response: The proposal to submit scientific justification for extrapolation of data and information for the "Hematopoietic Subsyndrome of Acute Radiation

Syndrome" indication in section 5.3.5.4 of the planned 351(k) BLA is acceptable. However, as this indication is protected by an unexpired period of orphan drug exclusivity, the Agency will not be able to approve the proposed product for this indication until the orphan drug exclusivity expires.[1] See question and answer I.24 in the draft guidance for industry, New and Revised Draft Q&As on Biosimilar Development and the BPCI Act (Rev. 2) (Dec. 2018). As such, we recommend that the labeling submitted with your original 351(k) BLA not include the orphan-protected indication.

Question 13: The data listings planned to be provided in Module 5 shall represent subject level data which can be identified by site, since the first three digits of Subject ID represents site number (e.g. for Subject ID 101-001 where 101 represents site number). Also, the data will be presented chronologically both as site and as subject within these listings. Therefore, Lupin believes that separate files of subject level data listings by individual sites might not be necessary and a single PDF of current listings can be provided for review. Does agency agree with this approach?

FDA Response: The proposal to provide a single PDF of subject level data listings in Module 5 is acceptable. However, provide the document separately from the CSR and provide book markings by site and by subject.

With regard to the datasets, each dataset should contain a column for "SUBJID" and a separate column for "SITEID".

For the major efficacy and safety studies, in addition to the study data, we also have the following request.

1. **Provide executable SAS programs with adequate document(s) to allow FDA to derive the analysis datasets from the raw datasets you submitted.**

2. **Provide the SAS programs as well as format library files used for efficacy and safety data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.**

3. **Include all study protocols, amendments, and all minutes as well as related materials for discussion during IND meetings.**

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[1] For additional information concerning timing considerations for submitting a supplement with the goal of obtaining licensure soon after expiration of orphan exclusivity, please see FDA draft guidance for industry, Biosimilars and Interchange Biosimilars: Licensure for Fewer Than All Conditions of Use for Which the Reference Product Has Been Licensed (February 2020).

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Question 14: During the initial development of pegfilgrastim, Lupin has conducted phase 3 safety and efficacy study in patients with non-myeloid malignancies to meet the requirements of local health authority, DCG(I) (Drugs Controller General of India). In the BPD Type 2 meeting minutes received on November 4, 2016, FDA has stated that "the completed study in patients with non-myeloid malignancies conducted in India may not provide any relevant information to support a demonstration of bio-similarity to US-licensed Neulasta." Therefore, Lupin does not plan to provide earlier conducted India centric phase III safety and efficacy study in the planned 351(k) BLA application. Does agency concur with this proposal?

FDA Response: Your approach appears reasonable. You may nevertheless wish to include safety data and results from study LRP/PegGCSF/2011/001 in the BLA.

Additional CMC Comments:

1. 

2. **To facilitate the Agency's review of the critical intermediate (CI), drug substance, and drug product manufacturing process for LUBT 004 in your 351(k) submission, we recommend you provide the information for all attributes, parameters, or controls proposed for routine commercial manufacturing as well as those evaluated during development and validation, in the tabular format provided below. Please provide a separate table for each unit operation. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3R. Note, this Table does not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.**

Process parameter/ operating parameter/ in-process control (IPC)	Proposed Range for Commercial Manufacturing	Criticality classification [1]	Range assessed during process development studies	Validated Range	Clinical Study Range	Justification of the proposed commercial acceptable range[2]

[1]For example, critical process parameter, non-critical process parameter, as described in module 3.

[2]Provide a brief summary description (e.g., "development range", "validation range", or "platform experience"). To link to additional description for justification you may additionally include a link or reference to the appropriate section of the eCTD with more detail.

3. **To facilitate the Agency's review of the control strategy for LUBT 004, we recommend you provide information in your 351(k) submission for quality attributes and process and product related impurities for the critical intermediate (CI), drug substance and drug product in the following tabular format. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3R. These tables do not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3. Attributes that are deemed to not be critical should also be justified in the BLA with the reasoning for that categorization.**

Critical Quality attributes (including Process and Product related impurities for CI, DS and DP)	Impact[1]	Source[2]	Analytical method[3]	Proposed control strategy[4]	Justification of the proposed control strategy[5]

[1]What is the impact of the attribute, e.g., contributes to potency, immunogenicity, safety, efficacy.
[2]What is the source of the attribute or impurity, e.g., intrinsic to the molecule, fermentation, protein A column.
[3]List all the methods used to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attribute.
[4]List all the ways the attribute is controlled, e.g., in-process testing, validated removal, release testing, stability testing.
[5]Provide a brief verbal description. In addition, you may provide links or references to appropriate sections of the eCTD that provide more detail.

4. **To facilitate the Agency's assessment of the adequacy of the proposed commercial release specifications of LUBT 004, we recommend you provide information in your 351(k) submission for each release specification in the tabular format provided below. Please provide a separate table for LUBT 004 CI, DS, and DP, as described below. Each release specification should be described in a separate row. Add additional rows for additional release specifications, as needed. In general, include footnotes for each column of grouped results to indicate which lot numbers were used for each calculation of minimum-maximum range, and provide the correct number (n=?) in the table also. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3R. These tables do not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.**

Release Specification for LUBT 004 Critical Intermediate (CI)							
Attribute	**Analytical Method**	**Proposed Commercial Release acceptance criteria**	**Release results for developmental batches (n=?) (min-max)**	**Release results for DS batches[a] (n=?) used in clinical studies (min-max)**	**Release results for DS PPQ batches (n=?) (min-max)**	**Release results for all lots[b] made using commercial process (n=?) (min-max)**	**Justification of specification (e.g. clinical experience, manufacturing capability, etc.)**

a. Include batches of different scale if the batch was used in any clinical testing. List each of the batch numbers included as footnote in the table.

b. Include all lots with available release data that were manufactured following the proposed commercial process. Include a list of the batch numbers included in analysis as a footnote in the table.

Release Specification for LUBT 004 Drug Substance							
Attribute	**Analytical Method**	**Proposed Commercial Release acceptance criteria**	**Release results for developmental batches (n=?) (min-max)**	**Release results for DS batches[a] (n=?) used in clinical studies (min-max)**	**Release results for DS PPQ batches (n=?) (min-max)**	**Release results for all lots[b] made using commercial process (n=?) (min-max)**	**Justification of specification (e.g. clinical experience, manufacturing capability, etc.)**

a. Include batches of different scale if the batch was used in any clinical testing. List each of the batch numbers included as footnote in the table.

b. Include all lots with available release data that were manufactured following the proposed commercial process. Include a list of the batch numbers included in analysis as a footnote in the table.

Release Specification for LUBT 004 Drug Product							
Attribute	**Analytical Method**	**Proposed Commercial Release acceptance criteria**	**Release results for nonclinical and developmental DP batches (n=?) (min-max)**	**Release results for clinical DP batches[a] (n=?) (min-max)**	**Release results for DP PPQ batches (n=?) (min-max)**	**Release results for all DP lots[b] made using commercial process, including PPQ lots**	**Justification of specification (e.g. clinical experience, manufacturing capability, etc.)**

						(n=?) (min-max)	

a. Include all batches used in any clinical testing, regardless of scale, process, or manufacturing location, etc. List each of the batch numbers included as footnote in the table.

b. Include all lots with available release data that were manufactured following the proposed commercial process. Include a list of the batch numbers included in analysis as a footnote in the table.

5. To facilitate the Agency's assessment of the adequacy of the stability specifications of LUBT 004 CI, DS and DP, we recommend you provide stability information in your 351(k) submission for storage at recommended condition for each stability specification in the example tabular format provided below. Please provide a separate table for LUBT 004 CI, DS and DP, as described below. Each stability specification should be described in a separate row. Add additional rows for additional stability specifications, as needed. If any stability specifications are different than the corresponding release specification for an analytical method that is used for both, then provide justification why different acceptance criteria are proposed for release and stability. Include footnotes to the tables to list the batch numbers that were used in each assessment, and justify any lots excluded from the assessment. Consider the data from all stability time points, not only release and end of proposed shelf-life. If a lot has not completed stability testing to the end of the proposed shelf-life, include data from all time points that are currently available for that lot in the evaluation. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3R. These tables do not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.

Stability Specification for LUBT 004 CI/DS/DP				
Attribute	**Analytical Method**	**Stability acceptance criteria**	**Stability results for batches stored at intended storage temperature (n=?)** **Min – Max (Range for all available data from time 0 to proposed end of shelf life or currently available)**	**Justification of specification (e.g. clinical experience, manufacturing capability, etc.)**

6. **In your in your 351(k) submission, provide an evaluation of extractables and leachables, including a risk assessment, for CI, DS, and DP. The BLA should include information that addresses the risk from potential leachables from the CI, DS and DP Container Closure System (CCS) over the shelf-life of your product. The leachables studies may be performed as part of your stability protocol to support CI, DS and DP expiry. Analysis of leachables should include organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS), semi-volatile (e.g., GC-MS), and metals (e.g., ICP-MS) species including their chemical identification and quantitation. Additional information regarding extractables and leachables should be provided per FDA Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics (1999).**

   A separate evaluation is also required for the potential generation of in-process leachables for CI, DS and DP as a result of the product contact to equipment including disposables such as filters, containers, and bags. Data from a risk assessment should be provided to assure patient safety if in-process leachables are identified. However, testing might not be required (or necessary) if you provide scientific justification that the downstream purification/ process steps are expected to clear any potential in-process leachables.

7. **Your shipping qualification studies for CI, DS and DP should include an assessment of product quality before and after shipment and be performed with product that is representative of the commercial manufacturing process, formulation, and container closure. Include in your original in your 351(k) submission results from shipping validation studies performed**

to support the physico-chemical stability of CI, DS and DP. These studies should assess the impact of worst-case shipping conditions and potential temperature excursions on the critical quality attributes of the product and represent the spectrum of allowed packing arrangements of product within any secondary/tertiary packaging also. Include a summary table of all shipping lanes for LUBT 004 from time of CI and DS shipping to all subsequent locations through DP manufacturing, labeling, packaging, etc. until the final product is ready for distribution. Include a description of any intermediate storage facilities where product may also be shipped for storage throughout this process, as applicable. Summarize for each shipping lane details of distance, method of transportation, and duration of the shipment, and indicate and justify which shipping validation data support that shipping lane.

8. **To facilitate the Agency's assessment of the suitability of the analytical methods for release and stability testing of LUBT 004 CI, DS, and DP and for in-process test methods, provide in your 351(k) submission summarized results of method validation in the tabular format provided below. Please provide a separate table for each analytical method, as described below. Each parameter, e.g. specificity, precision, accuracy, etc. should be described in a separate row. Add additional rows for additional parameters, as needed. Study design should include a brief description of the testing material (batch information), the number of tests (e.g., the number of replicates, runs, plates, analysts, etc., if applicable), design of the experiment, approach of data reporting, and other important overview information regarding the validation of that parameter, as needed. Indicate in the table title the name of the method and all applicable programs where it is used such as CI release/stability, DS release/stability, DP release/stability, or in-process testing.**

Summary of Validation Results for (insert Method) used for CI/DS/DP release/stability, in-process testing, etc.			
Location of QC commercial testing site:		**Location where method was validated[a]:**	
System Suitability Acceptance Criteria:			
Parameter	**Study Design**	**Acceptance Criteria**	**Validation Results**
a: Provide a reference to supporting information and data in the BLA for method transfer, as applicable, for methods that were validated in a different site than where they will be tested for commercial QC testing.			

9. **Provide in your 351(k) submission the following information in a completed table like the one below for all drug master files (DMFs) referenced in your biologics license application:**

DMF #	DMF Type	DMF Holder	Item referenced	Link to Letter of Authorization	Comments (if needed)

Immunogenicity

10. **Currently the data relevant to the assessment of immunogenicity are dispersed throughout different locations of the eCTD including 2.7.4 Summary of Clinical Safety, 5.3.1.4 Reports on Biopharmaceutical Studies and 5.3.5 Reports of Efficacy and Safety Studies. For the BLA file we recommend that the applicant provide the Integrated Summary of Immunogenicity in eCTD section 2.7.2.4 Special Studies or Section 5.3.5.3 Reports of Analysis of Data from More than One Study. This Integrated Summary of Immunogenicity should provide:**

    a) **Immunogenicity Risk Assessment - This section should provide a concise immunogenicity risk assessment specific to the therapeutic product.**

    b) **Tiered strategy and Bioanalytical Assays - This section should provide details on the tiered immunogenicity strategy that applicant followed and validation summaries for the various immunogenicity assay methods that were used along with links to method development and validation reports for relevant immunogenicity assays used.**

    c) **Clinical Study Design and Sampling Strategy - This section should provide the immunogenicity sampling plan(s) for all clinical studies that had immunogenicity assessment performed. This section should include as justification for pre-treatment, in-treatment, and post-treatment sampling time points for immunogenicity and pharmacokinetics, where applicable.**

    d) **Clinical Immunogenicity Data Analysis - This section should provide summary results of immunogenicity analyses for all clinical studies having immunogenicity component.**

Additional CMC Microbiology Comments:

The FDA is providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(k) BLA submission.

All facilities should be registered with the FDA at the time of the 351(k) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance critical intermediate, the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the 351(k) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance and drug substance critical intermediate. The information should include, but not be limited to the following:

- **Endotoxin removal steps should be clearly identified in the manufacturing process description (3.2.S.2.2). Endotoxin removal validation data obtained during manufacture of the process performance qualification lots (PPQ) should be provided in section 3.2.S.2.5.**

- **Justify the presence of any antibiotics that are used in the growth media for the fermentation production phases. Use of antibiotics during fermentation production is not recommended unless justified and should be removed from fermentation media, if feasible.**

- **Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).**

- **Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).**

- **Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels**

before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).

- **Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).**

- **Information and summary results from the shipping validation studies (3.2.S.2.5).**

- **Drug substance and drug substance critical intermediate bioburden and endotoxin release specifications (3.2.S.4).**

- **Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).**

The CMC Drug Product section of the 351(k) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry "Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

- **Identification of the manufacturing areas and type of fill line (e.g. open, RABS, isolator), including area classifications.**

- **Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.**

- **Parameters for filling and plunger placement for the pre-filled syringes.**

- **A list of all equipment and components that contact the sterile drug product (i.e. the sterile-fluid pathway) with the corresponding method(s) of**

sterilization and depyrogenation, including process parameters. The list should include single-use equipment.

- **Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.**

- **Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.**

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

- **Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.**

- **Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.**

- **In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.**

- **Isolator decontamination summary data and information, if applicable.**

- **Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.**

- **Information and summary results from shipping validation studies. For prefilled syringes, the effects of varying air pressure on pre-filled syringe plunger movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data demonstrating that the pre-filled syringe plunger movement during air transportation does not impact product sterility.**

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- **Container closure integrity testing. System integrity should be demonstrated initially and during stability. Data demonstrating the maintenance of container closure integrity after the assembly of the pre-filled syringe should be included. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (b) (4) Container closure integrity testing should be performed in lieu of sterility testing for stability samples every 12 months (annually) until expiry.**

- **Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers.**

- **Provide full descriptions and validation of non-compendial microbial methods.**

- **Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).**

- **Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> Bacterial Endotoxin Test (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time.**

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The original 351(k) application will be subject to "the Program" under BsUFA II. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions regarding the approach to developing the content for risk evaluation and mitigation strategies (REMS), where applicable, patient labeling (e.g., Medication Guide and Instructions For Use) 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.

Finally, in accordance with the BsUFA II agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on the Program is available at FDA.gov.[2]

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. SUMMARIZE DISCUSSION AND AGREEMENTS

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 regarding the approach to developing the content for a REMS, where applicable, patient labeling (e.g., Medication Guide and Instructions for Use) and, where applicable, the development of a Formal Communication Plan was held and it was concluded that TEXT.

- 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) (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 a pediatric assessment to support dosing, safety, and

[2] https://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm

effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

Section 505B(l) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived, deferred, or inapplicable.

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (iPSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed iPSP prior to initiating your comparative clinical study.

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an iPSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the iPSP. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive iPSP that addresses each indication. For indications for which the labeling for the reference product contains adequate pediatric information, you may be able to fulfill PREA requirements by satisfying the statutory requirements for biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from the reference product to your proposed product (see question and answer I.16 in the draft guidance for industry, *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act*. For conditions of use for which the reference product does not have adequate pediatric information in its labeling, a waiver (full or partial), or a deferral, may be appropriate if certain criteria are met.

After the iPSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3) of the FD&C Act. For additional guidance on the timing content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*[3]. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended

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)[4] and 201.57[5] 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[6] and Pregnancy and Lactation Labeling Final Rule[7] 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

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4 http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1

5 http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1

6 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm 084159.htm

7 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

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*.[8]

In addition, you should review the FDA guidance for industry *Labeling for Biosimilar Products* (July 2018).

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

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

[8] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Your proposed 351(k) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[9]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[10]

MANUFACTURING FACILITIES

All facilities should be registered with FDA at the time of the 351(k) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Manufacturing and testing facilities will be subject to the CGMP standards as described in 21 CFR 601.20, including but not limited to the good manufacturing practice requirements set forth in 21 CFR 210, 211, and 600 of this chapter.

Manufacturing facilities should be in operation and manufacturing the product under review during the inspection 2-7 months after the submission of the BLA. A manufacturing schedule for the drug substance and the drug product should be provided in Module 1 of the BLA to facilitate planning of pre-approval inspections during the review cycle. For a BLA submission, when providing the preliminary manufacturing schedule, we encourage you to bear in mind the anticipated time frame for the latecycle meeting for applications subject to "the Program" under BSUFA II.

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

[9] http://www.fda.gov/ectd
[10] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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, 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[11] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[12]. 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

[11] https://www.fda.gov/media/84223/download
[12] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identificationmanufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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* (February 2018) and the associated 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*.

RECOMMENDATIONS FOR FORMATTING OF CLINICAL PHARMACOLOGY SUBMISSIONS FOR APPLICATIONS

If you are planning to include a clinical pharmacology study as part of your 351(k) BLA marketing application, we have the following general best practice recommendations for you to keep in mind as you prepare your submission, including guides for formatting your submission.

1. As it relates to clinical pharmacology-related sections of the application, apply the following advice when preparing the 351(k) BLA:
    a. Include the rationale for the selected dose used in the PK (and PD similarity, when applicable) study(ies) in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).
    b. Include a summary evaluation of the impact of immunogenicity on the activity (e.g., efficacy/PD), safety, and pharmacokinetics, as is applicable, for the studies included in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).
    c. Present the PK (and PD, when applicable) parameter data as geometric mean with coefficient of variation, mean ± standard deviation, and median with range in the study reports and throughout the BLA.
    d. Provide analysis data sets for all concentration-time and derived PK (and PD, when applicable) 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.
2. Include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:

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.

3. Submit all PK (and PD, when applicable) bioanalytical method validation reports and bioanalytical study reports. In addition, complete the summary tables using the templates available in the 'Bioanalytical Methods Templates' Technical Specifications Document[10] to provide the information regarding the bioanalytical Methods for pharmacokinetic and/or biomarker assessments used in clinical pharmacology studies and their life-cycle information pertaining to the studies. Submit the tables in the Appendix of the Summary of Biopharmaceutics locatedin eCTD 2.7.1.

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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