

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761219Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 135944

**MEETING REQUEST-
WRITTEN RESPONSES**

Celltrion, Inc.
c/o Parexel International
4600 East West Highway
Suite 350
Bethesda, MD 20814

Attention: Ryan Zettle, PharmD, MBA
Senior Consultant

Dear Dr. Zettle:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CT-P17.

We also refer to your submission dated June 9, 2020, containing a meeting request. The purpose of the requested meeting was to seek feedback on the format and content of your future BLA submission under section 351(k) of the Public Health Act.

Further reference is made to our Meeting Granted letter dated June 30, 2020, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your June 30, 2020, background package.

If you have any questions, call Sadaf Nabavian, Regulatory Project Manager, at (301) 796-2777.

Sincerely,
{See appended electronic signature page}
Sadaf Nabavian, PharmD
CDR, US Public Health Service
Rheumatology and Transplant Medicine
Division of Regulatory Operations for
Immunology and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Written Responses



WRITTEN RESPONSES

Meeting Type: Biosimilar
Meeting Category: BPD Type 4

Application Number: IND 135944

Product Name: CT-P17
Indication: CT-P17 is being developed for the same indications as those approved for US-licensed Humira

Sponsor: Celltrion, Inc./Parexel International (U.S. Agent)
Regulatory Pathway: 351(k) of the Public Health Service Act

1.0 BACKGROUND

Celltrion/Parexel International (U.S. Agent) submitted a BPD Type 4 meeting request on June 9, 2020, as Written Response Only to obtain feedback on the content and format of a 351(k) BLA for CT-P17, as a proposed biosimilar to US-licensed Humira.

Celltrion/Parexel question is in ***bold italic***; FDA's written response is in normal font. FDA may provide further clarifications of, or refinements and/or changes to these written responses based on further information provided by Celltrion/Parexel 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 QUESTIONS AND RESPONSES

Question 1:

Does the FDA agree with the list of documents to be submitted in Module 1 of the initial Biologics License Application (BLA) for CT-P17 under section 351(k)?

FDA Response:

Yes, we agree.

Question 2:

Does the FDA agree with the proposed structure and format of the Drug Product Section (3.2.P) and that the information to be included in the Regional Information Section (3.2.R) will be adequate to allow review of the BLA? Is there a package we could assemble (e.g. validation protocols and reports, batch records, assay data, etc.) that may eliminate the need for an on-site inspection or facilitate a remote inspection? Please provide guidance.

FDA Response:

The proposed structure and format for 3.2.P Drug Product and 3.2.R Regional Information appear acceptable. See Additional Product Quality Comments below. The proposed structure of the device-related information in the BLA appears reasonable. We recommend that you include a reviewer's guide in Section 1.2 that provides a high-level overview (with reference links) of the submission's content. For additional information on the format of the BLA, please see the 2018 FDA Guidance for Industry *Providing Regulatory Submission in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (<https://www.fda.gov/media/93818/download>).

FDA will determine whether Pre-License Inspections (PLIs) or review of manufacturing site records under Section 704(a)(4) of the FD&C Act are needed at the time of the BLA submission. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of PLIs during the review cycle.

Question 3:

Does the Agency agree that CELLTRION will not be required to include a Risk Evaluation and Mitigation Strategies (REMS) as part of 351(k) BLA for CT-P17?

FDA Response:

Yes, we agree that the inclusion of a REMS is not required for filing of your 351(k) BLA submission.

Question 4:

CELLTRION intends to prepare and submit the nonclinical and clinical data in a standardized data format such as CDISC, respectively at the initial BLA. Does the Agency agree with the proposed format and location of the clinical datasets?

FDA Response:

Yes, we agree with your proposal.

Question 5:

Does the Agency agree with CELLTRION's plan to locate the document for Integrated Summary of Immunogenicity in CTD section 2.7.2.4 (Special Studies)?

FDA Response:

You may submit the immunogenicity risk assessment in section 2.7, Clinical Summary. The Integrated Summary of Immunogenicity as recommended in Section VIII

Documentation of the 2019 FDA Guidance for Industry: *Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection* should be submitted to eCTD Section 5.3.5.3 Reports of Analysis of Data from More than One Study.

Additional Product Quality Comments:

1. To facilitate our review of the DS and DP manufacturing processes for CT-P17, provide the information for process parameters and in-process controls, as applicable, in the following tabular format. Provide a separate table for each unit operation. The tables should summarize information from module 3 and may be submitted either to module 3R or module 1.

Process Parameter/ Operating Parameter/ In- Process Control	Proven Acceptable Range/ Control Limits/ Targets ¹ for Commercial Manufacturing Process	Criticality Classifica tion ²	Characterized Range/ Control Limits/ Targets ¹ tested in Process Development Studies	Manufactured Range/ Control Limits/ Targets ¹ used for Clinical Study Lots	Manufactured Range/ Control Limits/ Targets ¹ used in Process Validation	Justification of the Proposed Commercial Acceptable Range ³	Comment ⁴
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¹As applicable.

²For example, critical process parameter, key process parameter, non-critical process parameter, as described in module 3.

³This could be a brief verbal description and/or links to the appropriate section of the eCTD.

⁴Optional.

2. To facilitate our review of the control strategy for CT-P17, provide information for quality attributes and process- and product- related impurities for the DS and DP in the following tabular format. The tables should summarize information from module 3 and may be submitted either to module 3R or module 1.

Quality Attributes and Process and Product Related Impurities for DS and DP	Criticality Classification ¹	Impact ²	Source ³	Analytical Method ⁴	Proposed Control Strategy ⁵	Justification of the Proposed Control Strategy ⁶	Comment ⁷
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¹For example, critical quality attribute or non-critical quality attribute.

²What is the impact of the attribute, e.g. contributes to potency, immunogenicity, safety, efficacy.

³What is the source of the attribute or impurity, e.g. intrinsic to the molecule, fermentation, protein A column.

⁴List 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.

⁵List all the ways the attribute is controlled, for example, in-process testing, validated removal, release testing, stability testing.

⁶This could be a brief verbal description and/or links to the appropriate section of the eCTD.

⁷Optional.

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3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The original 351(k) application will be subject to “the Program” under BsUFA II. Therefore, there should be agreement with the 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.

If you 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.¹

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 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

¹ <https://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm>

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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 draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*². 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

² <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended>

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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)³ and 201.57⁴ 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 Information⁵ and Pregnancy and Lactation Labeling Final Rule⁶ 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.

³ http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1

⁴ http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/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.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

⁶ <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>

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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 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*.⁷

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

⁷ 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>.

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of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

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.

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 late-cycle 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 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 356h⁸ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁹. 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* (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

⁸ <https://www.fda.gov/media/84223/download>

⁹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

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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 $\pm$ 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 Document¹⁰ 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 located in eCTD 2.7.1.

¹⁰ <https://www.fda.gov/media/131425/download>

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/s/

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