

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761338Orig1s000

761338Orig2s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



BLA 761338

MEETING MINUTES

Celltrion, Inc.
c/o Parexel International
Attention: Ally Danta
Regulatory Affairs Consultant
2520 Meridian Parkway, NC 27713

Dear Ally Danta:

Please refer to your Biologics License Application (BLA) under section 351(k) of the Public Health Service Act for CT-P43.

We also refer to the meeting between representatives of your firm and the FDA on November 14, 2024. The purpose of the meeting was to discuss the September 30, 2024, Complete Response letter (CRL) and Celltrion's request for resuming first cycle review or, alternatively, expediting review of its response to the CRL as part of a second cycle review.

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

If you have any questions, email me at Howard.VanHornIII@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

H. F. Van Horn III, PharmD, MBA
Senior Regulatory Project Manager
Division of Regulatory Operations for
Dermatology and Dentistry
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosures: Meeting Minutes
Applicant's Meeting Material



MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: BPD Type 1

Meeting Date and Time: November 14, 2024, 2:00 – 3:00 PM EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room 1415
Silver Spring, MD 20903

Application Number: BLA 761338
Product Name: CT-P43
Indication: Same as US-licensed Stelara

Applicant Name: Celltrion, Inc.
Regulatory Pathway: 351(k) of the Public Health Service Act

Meeting Chair: Tatiana Oussova, MD, MPH
Meeting Recorder: LCDR Susan Rhee, PharmD

FDA ATTENDEES

IN-PERSON

Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDD
Frances Namuswe, Supervisor, Division of Product Quality Assessment XV/Office of Product Quality Assessment III (OPQA III)
Hailin (Sheena) Wang, PhD, Team Lead, OPQA III
Virginia Carroll, PhD, Team Lead, Office of Pharmaceutical Manufacturing Assessment (OPMA)
LCDR Susan Rhee, PharmD, Chief, Project Management Staff, Division of Regulatory Operations for Dermatology and Dentistry, (DRO – DD)
Stefanie Kraus, JD, MPH, Senior Regulatory Counsel, Office of Regulatory Policy (ORP)
Angela LaPier, JD, Regulatory Counsel, Office of Therapeutic Biologics and Biosimilars (OTBB)

VIRTUAL

Amy Weitach, DO, MS, Clinical Team Lead, DDD
Maryjoy Mejia, MD, Clinical Reviewer, DDD
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Inflammation and Immune Pharmacology (DIIP)
Ping Ji, PhD, Clinical Pharmacology Biosimilar Scientific Lead, DIIP
Sanjida Mahjabeen, PhD, Staff Fellow, DIIP

Wanjie Sun, PhD, Lead Mathematical Statistician, Division of Biometrics VIII (DBVIII)
Guoying Sun, PhD, Senior Mathematical Statistician, DBVIII
Erika Pfeifer, PhD, Supervisory Microbiologist, OPMA
Joao Pedras-Vasconcelos, PhD, Product Quality Reviewer, OPQA III
Susan Kirshner, PhD, Division Director, OPQA III
Melinda Bauerlien, MS, Senior Regulatory Business Process Manager, Division of
Regulatory and Business Process Management I (DRBPMI)
Jiangsong Jiang, PhD, Reviewer, OPMA
Mustafa Ünü, PhD, JD, Director of Policy Staff, OTBB
Nina Brahme, PhD, MPH, Scientific Reviewer, OTBB
Jacquelyn Rosenberger, PharmD, RAC, Team Lead, Project Management, OTBB
Frances Andrada, MSN, MPH, CRNP, FNP-BC, Scientific Reviewer, OTBB
Jessica Tyson, PhD, MPH, RAC, Science Policy Analyst, OTBB
Melissa Sage, Formal Dispute Resolution Program Manager, Office of Executive
Programs (OEP)
Shruti Modi, JD, Regulatory Counsel, Division of Regulatory Policy, Office of New Drug
Policy
CAPT Renmeet Grewal, PharmD, MS, RAC, Director, Project Management Staff,
Division of Regulatory Operations for Immunology and Inflammation (DRO – II)
H. F. Van Horn III, PharmD, MBA, Senior Regulatory Health Project Manager, DRO –
DD

SPONSOR ATTENDEES

CheHwee Park, MSc, Executive Vice President
Min Kyoung Jeon, PhD, Senior Director
Jong Hwan Kim, MSc, Senior Manager
Hyun Su Park, MSc, Senior Manager
Yun Kyung Cho, MSc, Manager
HyoJin Kim, PharmD, Manager
Yelin Jee, PharmD, Associate

(b) (4)

1.0 BACKGROUND

On June 30, 2023, Celltrion, Inc. (Celltrion), submitted BLA 761338 under section 351(k) of the Public Health Service Act for CT-P43, a proposed interchangeable biosimilar to US-licensed Stelara. On September 30, 2024, FDA issued a Complete Response letter (CRL). On October 23, 2024, Celltrion requested a biosimilar biological product development (BPD) Type 1 meeting to discuss its request for recission of the

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

CRL and resuming first cycle review or, alternatively, expediting review of its response to the CRL as part of a second cycle review. Celltrion currently seeks resolution at the Division level.

FDA sent Preliminary Comments to Celltrion, Inc. on November 12, 2024.

FDA may provide further clarifications of, or refinements and/or changes to the responses and the advice provided at the meeting based on further information provided by Celltrion, Inc. 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

2.1. Regulatory

FDA Introductory Comment:

The meeting request indicates that one of the objectives of the meeting is to “seek resolution of the issues at the Division level consistent with the recommendations in FDA’s guidance on Formal Dispute Resolution: Sponsor Appeals Above the Division Level (May 2019) before submitting a request for formal dispute resolution.”¹ If you intend to pursue formal dispute resolution, please note that the guidance states that formal dispute resolution procedures “are intended to promote rapid and fair resolution of scientific and/or medical disputes between a sponsor and CDER or CBER.”² If the questions you raise are framed as procedural questions and not scientific or medical, they might not be appropriate for formal dispute resolution. If you would like to request ombudsman assistance at any time regarding any issues, including the appropriate process for elevating this dispute, you may contact the CDER Ombuds at CDEROmbuds@fda.hhs.gov.³

Sponsor Introductory Discussion:

The meeting started with Celltrion’s representative presenting information in the attached slides in addition to reiterating points included in the meeting package.

Question 1:

Because the review issues listed in the CRL could have and should have been raised before the initial BsUFA goal date of June 30, 2024, why did FDA not communicate

¹ BPD Type 1 Meeting request, page 4

² See FDA’s Guidance for industry and review staff, *Formal Dispute Resolution: Sponsor Appeals Above the Division Level* at p. 2 available at: <https://www.fda.gov/media/126910/download>. See also Section III.A. of this guidance which discusses the type of matters that are appropriate for the formal dispute resolution process under part 314.

³ <https://www.fda.gov/about-fda/cder-ombuds/when-and-how-contact-cder-ombuds>.

these issues before the goal date or in a CRL to CELLTRION on the goal date of June 30, 2024, pursuant to the BsUFA Commitment Letter?

FDA Response to Question 1:

We communicated with Celltrion before June 30, 2024, regarding issues that led to the deficiencies identified in the September 30, 2024, complete response letter (CRL). Specifically, we sent Information requests (IRs) related to the issues identified in the September 30, 2024, CRL to Celltrion on March 26, 2024, and May 3, 2024, respectively, during the review cycle. After we reviewed your responses to the March 26, 2024, IR that we received on April 2, 2024, we identified deficiencies that were communicated as deficiencies 1 and 2 in the September 30, 2024, CRL. Regarding your responses to the May 3, 2024, IR that we received on May 13, 2024, your responses did not sufficiently address the deficiencies cited in the IR, which were communicated as deficiencies 3 and 4 in the September 30, 2024, CRL.

As discussed at the late cycle meeting on April 19, 2024, following a CGMP inspection of Celltrion, Inc., Korea (FEI 3005241015), FDA conveyed certain deficiencies to the representative of the facility. On June 14, 2024, we sent you a letter indicating that we have identified deficiencies that preclude further discussion of labeling and anticipated postmarketing requirements (PMRs) and known postmarketing commitments (PMCs). As of June 30, 2024, there was an outstanding deficiency related to the inspection. The inspection was reclassified to Voluntary Action Indicated (VAI) on July 26, 2024, and therefore the September 30, 2024, CRL does not include such deficiency.

Importantly, as of June 30, 2024, there was also an ongoing scientific disagreement that precluded action at that time. Specifically, during the review cycle, one of the primary reviewers concluded that there were clinically meaningful differences between CT-P43 and US-Stelara that would preclude approval based on review of the safety data in the comparative clinical study. The review team carefully considered the issues raised by the reviewer and was not able to reach resolution by June 30, 2024. After a thorough reconsideration of the evidence, including by the cross-disciplinary team leader, the CRL issued on September 30, 2024, did not include any clinical deficiencies.

Discussion to Question 1:

See Sponsor Introductory Discussion. No further discussions.

Question 2:

Why did FDA wait until September 30, 2024, to communicate the outstanding review issues to Celltrion?

FDA Response to Question 2:

See FDA Response to Question 1.

Discussion to Question 2:

See Sponsor Introductory Discussion. No further discussions.

Question 3:

Does FDA agree that there is no law, regulation, or policy prohibiting FDA from withdrawing the CRL and resuming first cycle review so long as the decision to withdraw the CRL is not arbitrary or capricious or an abuse of discretion?

FDA Response to Question 3:

Pursuant to section 21 CFR 601.3(a), FDA determined that your application was not approvable in its present form and issued a CRL on September 30, 2024, identifying deficiencies that needed to be addressed. The basis for the CRL is not in dispute and FDA believes that the CRL is appropriate. Pursuant to 21 CFR 601.3(b), your options were to withdraw your application or to resubmit it. You resubmitted your application on October 16, 2024, and we are reviewing it.

Discussion to Question 3:

See Sponsor Introductory Discussion. No further discussions.

Question 4:

Will FDA reconsider issuance of the CRL and agree to withdraw the CRL based on procedural deficits and resume first cycle review? If so, will FDA agree to a new target goal date of December 17, 2024?

FDA Response to Question 4:

See *FDA Response to Question 3*.

Discussion to Question 4:

See Sponsor Introductory Discussion. No further discussions.

Question 5:

If FDA decides not to withdraw the CRL, given the delay in issuing the CRL and the limited scope of the information to be reviewed, will FDA agree to a second cycle target goal date of December 17, 2024?

FDA Response to Question 5:

We do not agree. FDA will conduct its review in accordance with the goal dates specified in the BsUFA III Commitment Letter.

Discussion to Question 5:

FDA explained that while the goal date specified in the BsUFA III Commitment Letter is 6 months, we do not anticipate that our review will require the full 6 months. The review team noted that they will be sending an information request shortly. Celltrion indicated that they will promptly respond. While FDA cannot commit to a specific goal date, we are actively reviewing the resubmission and continuing other review activities.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

4.0 ATTACHMENTS AND HANDOUTS

- Applicant's Meeting Material

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/

HOWARD F VAN HORN
12/04/2024 09:36:02 AM

IND 146085

**MEETING REQUEST-
WRITTEN RESPONSES**

CELLTRION, Inc
c/o Parexel International
Attention: Ally Danta
Senior Associate, Regulatory
2520 Meridian Parkway, Suite 200
Durham, NC 27713

Dear Ally Danta:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CT-P43.

We also refer to your submission dated March 20, 2024, containing a meeting request. The purpose of the requested meeting was to discuss the development plan regarding the necessity of (b) (4)

Further reference is made to our Meeting Granted letter dated April 3, 2024, 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 March 20, 2024 background package.

If you have any questions, call Qianyiren Song, Regulatory Project Manager, at 301-796-2581.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD FAAD
Director, Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research
US Food and Drug Administration

Enclosure: Written Responses

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

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/

JILL A LINDSTROM
05/18/2024 07:51:14 AM



IND 146085

MEETING PRELIMINARY COMMENTS

CELLTRION, Inc.
c/o PAREXEL International
Attention: Ally Danta
Senior Associate, Regulatory
2520 Meridian Parkway, Suite 200
Durham, NC 27713

Dear Ms. Danta:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CT-P43.

We also refer to your October 31, 2022, correspondence, requesting a meeting to discuss the ongoing development program for CT-P43.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, an electronic version of any materials to be presented and/or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, call Qianyiren Song, Regulatory Project Manager, at 301-796-2581.

Sincerely,

{See appended electronic signature page}

Shari L. Targum, MD, MPH, FACP, FACC
Acting Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments



PRELIMINARY MEETING COMMENTS

Meeting Type: Biosimilar
Meeting Category: BPD Type 2

Meeting Date and Time: January 30, 2023; 9:30 – 10:00 a.m., EDT
Meeting Location: Teleconference

Application Number: IND 146085
Product Name: CT-P43

Proposed Indication: CT-P43 is being developed for the same indication as approved for US-licensed Stelara

Sponsor: Celltrion, Inc.
Regulatory Pathway: 351(k) of the Public Health Service Act

1 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 January 30, 2023; 9:30 – 10:00 a.m., EDT, between Celltrion and the Division of Division of Dermatology and Dentistry. 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 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

The purpose of this Type 2 meeting is to obtain concurrence with the Agency on the proposed clinical study design to support a demonstration that CT-P43 is interchangeable with US-licensed Stelara.

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 Celltrion, Inc. 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 QUESTION AND RESPONSES

2.1. Clinical

Question 1:

CELLTRION proposes to conduct a Phase 3 randomized study in patients with moderate to severe plaque psoriasis comparing PK, efficacy and safety in subjects who receive switching treatment with US-licensed Stelara (US-Stelara) and CTP43 versus subjects who receive only US-Stelara. Does the FDA agree that the proposed study design is suitable to support a demonstration of interchangeability between CT-P43 and US-Stelara, in particular with specific respect to:

- a. Overall study design
- b. Study population and inclusion/exclusion criteria
- c. Regimen
- d. Study period
- e. Primary endpoints, statistical analysis of primary endpoints
- f. Secondary endpoints
- g. Sample size and equivalence margin

FDA Response to Question 1:

Your overall proposal is consistent with the FDA guidance document “Considerations in Demonstrating Interchangeability With a Reference Product” in general.

You intend to submit an original BLA seeking licensure of CT-P43 as a biosimilar to US-licensed Stelara. You also intend to submit a supplement to support demonstration of interchangeability for CT-P43.

The proposed clinical development program to support a demonstration that CT-P43 is biosimilar to US-licensed Stelara includes the following completed and ongoing clinical studies:

- CT-P43 1.1: A randomized, double-blind, parallel-group, single-dose, pharmacokinetic (PK) similarity study conducted in two parts.
 - Part 1: A randomized, double-blind, 2-arm, parallel group, single dose study in 30 healthy subjects weighing 60-90 kg to evaluate initial safety [treatment-emergent adverse events (TEAEs), additional PK, safety, and immunogenicity of CT-P43] compared to that of EU-approved Stelara.
 - Part 2: A randomized, double-blind, 3-arm, parallel group, single dose in 240 healthy subjects weighing 60-90 kg to demonstrate similar PK, safety, and tolerability of CT-P43, US-licensed Stelara, and EU-approved Stelara.

- CT-P43 3.1: A randomized, double-blind, 2-arm, parallel group study to compare efficacy, PK, immunogenicity, and safety between CT-P43 and EU-approved Stelara in 509 subjects with moderate to severe plaque psoriasis.

The clinical study you plan to conduct to support a demonstration that CT-P43 is interchangeable with US-licensed Stelara is the focus of this meeting:

CT-P43 3.2: A randomized, active-controlled, double-blind, multicenter, study to evaluate PK, efficacy, and overall safety, including immunogenicity, of treatment alternating US-licensed Stelara (45 mg) and CT-P43 (45 mg) compared to US-licensed Stelara (45 mg) in subjects with moderate to severe psoriasis.

During Study CT-P43 3.2, approximately 468 adult subjects with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy, will be treated with US-licensed Stelara 45 mg dosed at Weeks 0 and 4 (Lead-in Period). Prior to randomization at Week 16, Psoriasis Area Severity Index (PASI) assessment will be conducted. Subjects who do not achieve at least PASI 50 response will be discontinued from the study. Subjects achieving at least PASI 50 will be randomized in 1:1 ratio to either continue treatment with US-licensed Stelara or be assigned to the switching arm, with all subjects receiving the study drug every 12 weeks (Switching Period). Subjects in the switching arm will undergo treatment by alternating between the proposed interchangeable product (CT-P43) and US-licensed Stelara. Switching will occur at Weeks 16 (to CT-P43), 28 (to US-licensed Stelara), and 40 (to CT-P43).

Your proposed primary endpoints are maximum serum concentration (C_{max}) and area under the concentration-time curve (AUC_{tau}) between Week 40 and Week 52. You also propose PK-related secondary endpoints: time to maximum serum concentration (T_{max}) between Week 40 and Week 52 and trough concentration (C_{trough}) up to Week 52.

You propose the following secondary efficacy endpoints:

- PASI percent improvement from baseline through Week 52
- proportion of subjects achieving PASI 50/75/90/100 through Week 52
- static Physician's Global Assessment (sPGA) 0/1 at Week 52

Safety assessments include laboratory monitoring, immunogenicity, and hypersensitivity assessment.

a. Overall study design

The proposed overall study design is acceptable. We agree that subjects who do not achieve PASI 50 response at Week 16 be discontinued from further dosing.

However, we recommend that subjects who do not achieve PASI 75 at Week 28 also be discontinued from further dosing in order to protect non-responders from being exposed to the risks of treatment in the absence of clinically meaningful benefit.

b. Study population and inclusion/exclusion criteria

We agree with the proposed study population of adult subjects weighing between 60 to 90 kg with moderate to severe psoriasis who are candidates for phototherapy or systemic therapy [defined as a PASI score of ≥ 12 , body surface area (BSA) involvement $\geq 10\%$, and a sPGA score of ≥ 3].

c. Regimen

Subjects will receive a single subcutaneous injection of 45 mg/0.5 mL of US-Stelara via pre-filled syringe with safety guard (PFS) at Weeks 0 and 4, followed by one injection of 45 mg/0.5 mL US-Stelara or CT-P43 every 12 weeks. Your background package states that if a subject's weight changes to > 100 kg, the subject can receive 2 injections of 45 mg/0.5 mL US-Stelara or CT-P43 at the investigator's discretion.

The proposal to use the 45mg/0.5 mL PFS presentation for both dose levels is acceptable but will result in subjects >100 kg receiving twice as many injections. Perform safety, as well as efficacy, subgroup analyses for subjects ≤ 100 kg and >100 kg with particular attention to injection site reactions.

d. Study period

The durations of the lead-in and switching periods are acceptable.

e. Primary endpoints, statistical analysis of primary endpoints

We agree with your primary endpoints of area under the concentration-time curve over the dosing interval between Weeks 40 and 52 ($AUC_{\text{tau}, 40-52}$) and maximum serum concentration during the dosing interval Weeks 40 and 52 ($C_{\text{max}, 40-52}$). You proposed that the primary PK statistical analysis "will be analyzed in the PK set who received all 5 doses (full) of the study drugs (only 45 mg) and maintain weight ≤ 100 kg during the study. Patients who receive 90 mg at any visit will not be included in the primary PK analysis. Patients who weighted >100 kg at any visit at or after Week 16 but were administered 45 mg at the investigator's discretion will be discussed on a case-by-case basis at the blinded Data Review Meeting (DRM) before unblinding for inclusion in the primary PK analysis". This proposal is reasonable.

You proposed that “the statistical analysis of the log-transformed primary endpoints (AUC_{tau} and $C_{max, 40-52}$)” will be “An analysis of covariance (ANCOVA)... with a fixed effect of treatment (Switching vs. US-Stelara maintenance) and covariates as follows:

- Anti-drug antibody (ADA) status at Week 16 (categorical value)
- Body weight at Week 16 (continuous value)
- AUC_{tau} , 4-16 or C_{max} , 4-16 for the corresponding primary endpoint (continuous value)
- Disease activity by PASI score at Week 16 (pre-dose); Log-transformed ratio of PASI score at Week 16 over PASI score at Week 0 (continuous scale).”

Your proposed ANCOVA model is reasonable in general. We acknowledge that your proposal of using the log-transformed primary endpoints (AUC_{tau} and $C_{max, 40-52}$) is consistent with the recommendation of the FDA guidance document “Considerations in Demonstrating Interchangeability With a Reference Product.” However, the development of anti-drug antibodies for biosimilar products may affect the PK data distribution and make the rationale of log-transformation not applicable.

Consider conducting an interim analysis to evaluate the distribution of the primary endpoints to ensure that the proposed data transformation (log-transformation) is appropriate for this study. The planned interim analysis should follow appropriate statistical principles and be adequately pre-specified in the protocol. Should you use an alternative statistical approach, provide justification in your analysis plan. In addition, how to handle concentration values below the lower limit of quantification (LLOQ) should be clearly pre-specified in the protocol.

f. Secondary endpoints

Secondary efficacy endpoints of percent improvement from baseline in PASI score and sPGA 0/1 at Week 52 are acceptable. We do not agree with PASI 50. We recommend PASI 75/90/100.

Secondary PK endpoints of time to maximum serum concentration during the dosing interval ($T_{max, 40-52}$) and Trough concentration (C_{trough}) are acceptable. .”

The safety endpoints and monitoring plan are acceptable.

You proposed that “Analysis of secondary endpoints will be conducted for all patients including the patients who weighted >100 kg at any visit.” Your proposal

to include the patients who weighed >100 kg at any visit in analyses of secondary endpoints is reasonable.

You proposed to analyze efficacy endpoints in the Efficacy Set defined as all patients who are randomized and received at least 1 dose (full or partial) of the study drug (CT-P43 or US-Stelara, correct study drug administered according to the dosing schedule) during the Switching Period. We recommend you also analyze efficacy endpoints in the Per Protocol Set. The ICH E9 Statistical Principles for Clinical Trials Guidance states that,

“The full analysis set and the per protocol set play different roles in superiority trials (which seek to show the investigational product to be superior) and in equivalence or noninferiority trials (which seek to show the investigational product to be comparable). In superiority trials, the full analysis set is used in the primary analysis (apart from exceptional circumstances) because it tends to avoid over-optimistic estimates of efficacy resulting from a per protocol analysis. This is because the noncompliers included in the full analysis set will generally diminish the estimated treatment effect. However, in an equivalence or noninferiority trial, use of the full analysis set is generally not conservative and its role should be considered very carefully.”

No detailed descriptive statistical analysis plan (SAP) is provided for secondary endpoints. Details should be provided in the SAP.

g. Sample size and equivalence margin

You proposed that 175 patients in each group will provide 90% power to show PK similarity between Switching and US-Stelara maintenance groups using 90% CI (two one-sided alpha 0.05) approach based on 80-125% equivalence margin for the geometric mean ratio, a coefficient of variation (CV) of 70% and expected ratio of 1.0. With a 25% hypothesized drop-out rate, you proposed to enroll 486 patients.

The 80-125% equivalence margin is acceptable. It is consistent with the recommendation of the FDA Guidance “Considerations in Demonstrating Interchangeability With a Reference Product”.

Your sample size calculation is reasonable in general. If allowing a small deviation from the perfect expected geometric mean ratio 1, 175 patients in each group will still provide about 80% power if the expected ratio is 0.95 or 1.05, assuming the inter-subject CV is 70%. Provide your justification for an estimation of 70% CV.

Question 2:

Assuming the CT-P43 is demonstrated to be biosimilar to Stelara for all indications the Stelara is licensed for, does the FDA agree that the results of the

clinical studies suggested in this briefing document will be sufficient for justifying interchangeability of CT-P43 in all currently authorized indications of Stelara in the US?

FDA Response to Question 2:

Your approach to providing scientific justification for extrapolating data and information in your application to support licensure of CT-P43 under section 351(k) as an interchangeable biosimilar for each condition of use for which licensure is sought, appears reasonable. A final decision about the adequacy of any scientific justification will be made during review of the 351(k) application.

However, as previously discussed during a biosimilar product development (BPD) Type 2 meeting held on September 14, 2022, residual uncertainties remain based on the comparative analytical assessment (CAA) analysis, as well as the PK data generated in Study CT-P43 1.1 Part 2. The PK similarity between CT-P43 and US-Stelara and between CT-P43 and EU-Stelara has not been established. We reiterate our concern that the clinical data obtained from Studies CT-P43 1.1 and CT-P43 3.1 would not be sufficient to support a demonstration that there are no clinically meaningful differences between CT-P43 and US-Stelara because PK similarity has not been demonstrated and an adequate scientific bridge has not been established to support the relevance of clinical data generated with EU-Stelara to the assessment of biosimilarity.

(b) (4)

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

Please be advised that an original 351(k) BLA will be subject to “the Program” under BsUFA II. Therefore, at an appropriate time, you should request a BPD Type 4 (pre-351(k) BLA) meeting and 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.

Include in your BPD Type 4 meeting package your proposals for 1) the content of a complete application and 2) any minor components to be submitted within 30 days after your original submission. You should also include, as part of your meeting questions, a request for our agreement with your proposals.

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

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

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

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),

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

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 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*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.

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).

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

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.⁸

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cdereadata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁹ that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized

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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

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

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<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

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

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>.

⁸ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

⁹ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

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format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.¹⁰

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources¹¹ and the CDER/CBER Position on Use of SI Units for Lab Tests website found at FDA.gov.¹²

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.¹³

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 *for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.¹⁴

¹⁰ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

¹¹ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

¹²

<https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>

¹³ <http://www.fda.gov/ectd>

¹⁴ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

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

/s/

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01/27/2023 11:56:16 AM



IND 146085

MEETING MINUTES

CELLTRION, Inc.
c/o PAREXEL International
Attention: Ally Danta
Senior Associate, Regulatory
2520 Meridian Parkway, Suite 200
Durham, NC 27713

Dear Ms. Danta:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CT-P43.

We also refer to the meeting between representatives of your firm and the FDA on September 14, 2022. The purpose of the meeting was to discuss the ongoing development program for CT-P43.

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

If you have any questions, call Qianyiren Song, Regulatory Project Manager at 301-796-2581.

Sincerely,

{See appended electronic signature page}

Gordana Diglisic, MD
Associate Director for Therapeutic
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: BPD Type 2

Meeting Date and Time: September 14, 2022; 11:00 a.m. – 12:00 p.m. EDT
Meeting Location: Videoconference

Application Number: IND 146085
Product Name: CT-P43

Proposed Indication: CT-P43 is being developed for the same indication as approved for US-licensed Stelara

Sponsor: Celltrion, Inc.
Regulatory Pathway: 351(k) of the Public Health Service Act

Meeting Chair: Gordana Diglisic, MD
Meeting Recorder: Qianyiren Song, PharmD

FDA ATTENDEES

Gordana Diglisic, MD	Associate Director for Therapeutic Review, Division of Dermatology and Dentistry (DDD)
Amy Weitach, DO, MS	Clinical Team Leader, DDD
Maryjoy Mejia, MD	Clinical Reviewer, DDD
Chinmay Shukla	Clinical Pharmacology Scientific Lead, Division of Inflammation and Immune Pharmacology (DIIP)
Ping Ji, PhD	Clinical Pharmacology Biosimilar Scientific Lead, DIIP
Da Zhang, PhD	Clinical Pharmacology Reviewer, DIIP
Kathleen Fritsch, PhD	Biostatistics Reviewer, Division of Biometrics III
Archita Patel, PharmD, JD	Regulatory Counsel, Office of Therapeutic Biologics and Biosimilars (OTBB)
Michelle Luo, MD, PhD	Scientific Reviewer, OTBB
Cristina Ausin, PhD	Scientific Reviewer, OTBB
Chana Fuchs, PhD	Team Leader, Office of Biotechnology Products (OBP)
Jee Chung, PhD	Product Quality Reviewer (OBP)
Qianyiren Son, PharmD	Regulatory Health Project Manager, Division of Regulatory Operations for Dermatology and Dentistry (DRO – DD)

SPONSOR ATTENDEES

CELLTRION (CLT)

JaeHwee Park	Head of Regulatory Affairs Division
Min Kyoung Jeon	Head of Regulatory Affairs Department
Jong Hwan Kim	Head of Clinical Regulatory Affairs Department
Su Won Song	Team Leader of Regulatory Affairs
Kyung Ok Park	Team Leader of Clinical Regulatory Affairs
Hee Joung Son	Head of CMC Regulatory Affairs Department
Hyun Su Park	Team Leader of CMC Regulatory Affairs
Yunju Bae	Head of Clinical Planning 1 Department
Dabee Jeon	Team Leader of Clinical Planning 3
Il Sung Chang	Head of Biometrics Center
Tina Pyo	Team Leader of Clinical Statistics 1

(b) (4)

1.0 BACKGROUND

Celltrion Inc. is developing CT-P43 as a biosimilar product to US-licensed Stelara. The purpose of this BPD Type 2 Meeting was to discuss and obtain the Agency's feedback and advice on the adequacy of pharmacokinetic (PK) outcomes observed, the clinical data for the studies to be included in the initial Biologics License Application (BLA) application, BLA submission plan regarding drug product presentations and similarity design, etc.

FDA sent Preliminary Comments to Celltrion, Inc. on September 9, 2022.

FDA may provide further clarifications of, or refinements and/or changes to the responses and the advice provided at the meeting based on further information provided by Celltrion Inc. 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).

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2.0 QUESTION AND RESPONSES

Question 1:

In the previous BPD Type 2 meeting (Submitted on March 29, 2021, via SN0014), CELLTRION consulted on the comparative analytical assessment design for CT-P43 including four different presentations considered for the initial BLA as below.

- 45 mg/0.5 mL PFS for SC injection (45 mg SC PFS),
- 90 mg/1 mL PFS for SC injection (90 mg SC PFS),
- 45 mg/0.5 mL Vial for SC injection (45 mg SC vial), and
- 130 mg/26 mL Vial for IV injection (130 mg IV vial).

For the initial BLA submission, CELLTRION proposes to include only two strengths of CT-P43 (45 mg/0.5 mL and 90 mg/1 mL) presented in PFS due to changes in development schedule. The other presentations (45 mg SC vial and 130 mg IV vial) for CT-P43 are still under development and therefore not included in the initial BLA submission planned in this year. As such, the previously suggested design of comparative analytical assessment should be slightly modified. Considering this development plan, does the Agency agree that the proposed comparative analytical assessment to obtain the licensure of 45 mg SC PFS and 90 mg SC PFS is adequate?

FDA Response to Question 1:

Based on the information provided in Table 3 of the meeting package, the identified six lots (two process performance qualification (PPQ) lots at 45 mg/0.5 mL, 1 PPQ lot at 90 mg/mL, 2 clinical lots at 45 mg/0.5 mL and 1 clinical lot at 90 mg/mL) planned to be used in the comparative analytical assessment (CAA) could be sufficient if the following are demonstrated:

- a. Comparability between the two strengths, 45 mg/0.5 mL and 90 mg/mL prefilled syringes (PFS);
- b. Comparability between drug product (DP) lots manufactured at the clinical and the commercial manufacturing sites, (b) (4) Celltrion Pharm. Inc., Republic of Korea, respectively.

We note our concern with this plan and caution you that with this limited number of lots made up from different strengths, you are running a risk that any variations in the provided data that result in questions or uncertainties in the analysis of similarity could impact the ability to demonstrate that CT-P43 is highly similar to US-licensed Stelara. Additionally, for any DP quality attributes that are specific to a strength, having only 2 lots of 90mg/mL or only 4 lots of 45mg/0.5 mL strength would pose an issue for your plans on showing similarity. Lots used in the PK similarity study and the comparative clinical study should be included in the CAA study. It is not clear from your meeting package if your PK similarity study and comparative clinical study used only the 2 CT-P43 clinical lots identified, and if the US-licensed Stelara and EU- approved Stelara lots

used in the CAA are the ones that were used in the PK similarity and comparative clinical study.

You should verify that each of the proposed CT-P43 lots used in the CAA are independent lots made from different DS lots and made from independent fill activities or identify if any lots are not independent and are linked to the same drug substance (DS) lot.

The comparability study design for the DP manufacturing site change for commercial production as well as the details regarding the extent of manufacturing changes that will occur were not provided in the meeting package. Therefore, as a general advice, sufficient number of lots should be used to demonstrate comparability of the commercial DP lots to the clinical lots. In addition, we refer you to our previous advice on the number of PPQ lots that should be manufactured for the 90 mg/mL strength (FDA response Question 3 of the March 29, 2021, BPD Type 2 meeting).

Regarding the number of CT-P43 lots, the current information differs from the previous Biosimilar Biological Product Development (BPD) Type 2 meeting, March 29, 2021, Table 5 that showed a total of 10 independent DS and DP lots to be used for the CAA and an explanation was not provided for the exclusion of the additional DS lots. CAA data from DS lots that were not used to manufacture DP lots could also be used to attain a sufficient number of lots to help minimize or eliminate any differences in product quality attributes noted in the CAA obtained thus far, e.g., differences in oxidation (Met254), glycosylation (mannosylation, fucosylation, and sialylation), and charge variants. Note that for any lots manufactured to date that are not included in the CAA, including the PPQ lots at the intended commercial site, a justification should be provided for the exclusion of these lots from the CAA, and data provided to show comparability of these lots to the lots used in the CAA. The BLA should include DP lot genealogy for all CT-P43 lots included in the CAA as well as for the other CT-P43 lots to enable an appropriate analysis of the data available.

Meeting Discussion for Question 1:

The Agency expressed appreciation for the update and agreed that the number of lots would be sufficient to meet the minimal number of lots for the CAA.

Question 2:

CELLTRION conducted a three-way pharmacokinetics (PK) study in 241 healthy volunteers primarily to assess PK similarity between CT-P43, US- and EU-Stelara (Study CT-P43 1.1 Part 2). While the 90% confidence intervals (CIs) for the geometric mean ratio of C_{max} were within the prespecified margin of 80% to 125% in the pairwise comparisons between CT-P43, US- and EU-Stelara, the upper bounds of the 90% CIs for AUC_{0-inf} were over the 125% acceptance range between CT-P43 and US-/EU-Stelara, which the Sponsor considers is attributed to approximately 1.6-8.2% higher protein content measured in CT-P43 lots compared to US-Stelara lot used for the PK similarity study. Thus, CELLTRION conducted comprehensive root cause analyses to

identify factors that may impact the PK results as well as post-hoc ANCOVA analyses by using different covariates, all of which will be included in the initial BLA.

- 1) Does the Agency agree that the PK data generated in Study CT-P43 1.1 Part 2 together with the comprehensive investigation and additional analyses included in the briefing document with regards to the PK outcomes observed in Study CT-P43 1.1 Part 2 are sufficient to support the PK similarity between CT-P43 and Stelara?
- 2) The preliminary data from Study CT-P43 3.1 show comparable results. Does the Agency consider that the clinical data obtained from Studies CT-P43 1.1 and CT-P43 3.1 would be sufficient to assess biosimilarity of CT-P43 to US-Stelara based on the totality of evidence?

FDA Response to Question 2:

- 1) We do not agree. The PK similarity between CT-P43 and US-Stelara and between CT-P43 and EU-Stelara does not appear to be established as the upper bounds of the 90% CIs for AUC_{0-inf} were over the 125% acceptance criterion for those two pairwise comparisons in your original analysis. We do not accept the post hoc analysis in which the protein content was used as covariate because the 1.6-8.2% higher protein content in CT-P43 is unlikely to be the root cause of the observed higher exposure. The PK similarity study, along with the comparative analytical assessment, led to the residual uncertainties regarding our ability to conclude that CT-P43 could be biosimilar to US-Stelara.
- 2) Based on the CT-P43 1.1 study results provided in the briefing document, the PK similarity between CT-P43, US-Stelara, and EU-Stelara was not established. Hence, we are concerned that the clinical data obtained from Studies CT-P43 1.1 and CT-P43 3.1 would not be sufficient to support a demonstration that there are no clinically meaningful differences between CT-P43 and US-Stelara because PK similarity has not been demonstrated and an adequate scientific bridge has not been established to support the relevance of clinical data generated with EU-Stelara to the assessment of biosimilarity.

Meeting Discussion for Question 2:

The Agency explained that, from the CAA analysis, we had some residual uncertainties for which we are counting on the PK data to resolve, including the difference in charge where acidic variants were lower by 14% in CTP43 (in peaks 4a, 2, and 3) and identified as related to sialic acid content, and specifically the NGNA/NANA difference for which there is literature identifying that there are differences in immunogenicity due to pre-existing antibodies to NGNA in some people. Regarding antibodies to NGNA, the Agency asked whether the immunogenicity assays were designed to be able to detect ADAs to NGNA and the sponsor clarified that the assays were not. Therefore, the

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Agency suggested exploring the possibility of ADAs to NGNA as one potential cause for the observed PK difference that may also explain the negative ADA patient PK data.

The Agency acknowledged that there is difference in protein content between CT-P43 and US- licensed Stelara and EU- approved Stelara and the Agency also acknowledged the post-hoc analysis using protein content as a covariate. The Agency stated that the protein content difference of 1.6% to 8.2% is unlikely to be the sole cause to produce the observed difference in PK and encouraged the Sponsor to explore the effect of residual uncertainties that could also impact PK.

The Sponsor inquired if they could conduct another 3-way PK similarity study. The Agency responded that there is no objection to the conduct of a new 3-way PK similarity study but the Sponsor must provide a justification to support the acceptability of the data from new 3-way PK similarity study in lieu of the current PK similarity study by providing details of the difference in quality attributes of the products used in the old and new PK similarity studies.

The Sponsor inquired whether the filing of BLA would not be possible (i.e., Refuse to file) based on the current analytical and clinical data package. The Agency reiterated the residual uncertainties and noted those are major issues. The Agency added that the decision of whether to file the BLA will be made after receipt of the application.

Question 3:

As agreed by FDA in BPD Type 2 meeting held on February 26, 2020, CELLTRION intends to provide the data up to Week 28 for all subjects from Study CT-P43 3.1 which will include primary efficacy analysis (i.e., mean percent improvement from baseline in Psoriasis Area and Severity Index [PASI] score at Week 12) and 12 weeks of safety and immunogenicity data following the single transition (from reference product to CT-P43) together with datasets in standardized CDISC format (e.g., SDTM and ADaM) at the initial BLA submission. In addition, the follow-up safety data up to Week 52 for all subjects from Study CT-P43 3.1 will be provided in Section 5.3.5.3 Safety Update at the 4-Month Safety Update. Does the Agency agree and have any feedback with the proposed approach?

FDA Response to Question 3:

While we consider your proposal to provide data from the comparative clinical study (CT-P43 3.1) for all subjects up to Week 28 at the initial BLA submission and follow-up safety data for all subjects up to Week 52 at the 4-Month Safety Update, acceptable, you will first need to address residual uncertainties from the comparative analytical assessment and PK similarity study. Refer to FDA Responses to Questions 1 and 2.

Meeting Discussion for Question 3:

No discussion occurred.

Question 4:

As mentioned in Question 1, for the initial BLA submission, CELLTRION proposes to include two strengths of CT-P43 (45 mg and 90 mg) presented in PFS that can administer the same dosage in the approved indications that use Stelara® 45 mg and 90 mg in PFS. Although the Stelara® USPI states that for pediatric Psoriasis patients (< 60kg) and for the initial treatment of Crohn's Disease (CD) and Ulcerative Colitis (UC) patients, Stelara® should be administered with 45 mg vial and 130 mg vial respectively, for maintenance of CD and UC, the USPI recommends administration (b) (4) 90 mg PFS. Consequently, CELLTRION, for the initial BLA, would like to exclude indication for pediatric psoriasis who weigh <60kg but include all the other approved indications of Stelara®, including CD and UC induction, and would like to know if this approach is acceptable to the US-FDA.

FDA Response to Question 4:

US-licensed Stelara is indicated for the treatment of patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. At time of the BLA filing, you intend to provide the pre-filled syringe presentations for subcutaneous (SC) dosing. However, the pre-filled syringes will only be appropriate for dosing patients weighing at least 60 kg. You intend to develop a separate vial presentation to allow for SC dosing in patients weighing less than 60 kg after the submission of your initial BLA. We have reviewed your amended iPSP. Formal communication providing the Agency's feedback is forthcoming.

Further, we acknowledge that you are considering including maintenance dosing of adult patients with moderate to severe Crohn's disease (CD) and ulcerative colitis (UC) in the label for CT-P43 as the proposed biosimilar to US-licensed Stelara. Although it is premature to comment on your proposal, we have the following preliminary comments:

Given that the dosing regimen for the treatment of CD and UC includes a single IV dose followed by continued treatment with the subcutaneous (SC) presentation, submission of data for the 130 mg vial presentation at the time of the initial BLA submission would be beneficial for ease of use in the clinical setting.

The issue of whether you could pursue a development plan and obtain licensure of your proposed product without an IV formulation, utilizing, for example, a maintenance regimen only for the treatment of CD and UC, would likely involve several considerations and review of additional information. For example, you may be asked to provide additional justification that such a development plan would be consistent with the statutory language in section 351(k)(2)(A)(i)(III) of the Public Health Service Act, which provides that "the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for a biosimilar product have been previously approved for the reference product." You may also wish to refer to Q.I.4, in the guidance for industry, Questions and Answers on Biosimilar Development and the BPCI Act

(Revision 2), which indicates that an applicant will not be able to obtain licensure of a proposed biosimilar product when a design difference in the delivery device or container closure system results in a condition of use (e.g. indication, dosing regimen) for which the reference product has not been previously approved. In addition, if you propose to omit information from the proposed labeling to pursue a maintenance regimen only for the treatment of CD and UC, further consideration would need to be given as to whether the omission of such information would be appropriate under section 351(k).

Meeting Discussion for Question 4:

The Agency reiterated the preliminary response and noted that submission of data for the 130 mg vial presentation at the time of the initial BLA submission would be beneficial for ease of use in the clinical setting. The Agency added that while it is premature to comment on the proposed plan, based on the information the Sponsor provided, the Agency has not identified an issue that would preclude filing with respect to pursuing the maintenance regimen for the treatment of CD and UC. However, a determination of whether to file the BLA will be made after the BLA is submitted.

Question 5:

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-P43?

FDA Response to Question 5:

Yes, we agree that inclusion of a Risk Evaluation and Mitigation Strategies (REMS) is not required for filing of your 351(k) BLA submission.

Meeting Discussion for Question 5:

No discussion occurred.

3.0 ADMINISTRATIVE COMMENTS**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

Please be advised that an original 351(k) BLA will be subject to “the Program” under BsUFA II. Therefore, at an appropriate time, you should request a BPD Type 4 (pre-351(k) BLA) meeting and 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.

Include in your BPD Type 4 meeting package your proposals for 1) the content of a complete application and 2) any minor components to be submitted within 30 days after your original submission. You should also include, as part of your meeting questions, a request for our agreement with your proposals.

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

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

Information on the Program is available at [FDA.gov](https://www.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 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

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

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*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>

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/cfcfr/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/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.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

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

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

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.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.⁸

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cdeler-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical

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>.

⁸ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁹ that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter

⁹ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

of your submission.

Additional information can be found at FDA.gov.¹⁰

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources¹¹ and the CDER/CBER Position on Use of SI Units for Lab Tests website found at FDA.gov.¹²

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.¹³

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.¹⁴

4.0 SPONSOR'S RESPONSE TO FDA PRELIMINARY COMMENTS

¹⁰ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

¹¹ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

¹²

<https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>

¹³ <http://www.fda.gov/ectd>

¹⁴ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

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/

GORDANA DIGLISIC
10/23/2022 09:27:21 AM

IND 146085

**MEETING REQUEST-
WRITTEN RESPONSES**

Celltrion, Inc.
c/o Parexel International
Attention: Ally Danita
Senior Associate
2520 Meridian Parkway, Suite 200
Durham, NC 27713

Dear Ms. Danita:¹

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CT-P43.

We also refer to your submission dated January 25, 2022, containing a meeting request. The purpose of the requested meeting was to discuss FDA feedback and advice on the selection of an IL-12 reporter assay for use as the potency assay.

Further reference is made to our Meeting Granted letter dated February 15, 2022, 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 January 25, 2022, background package.

If you have any questions, email: Krisine.Leahy@fda.hhs.gov, or call (240) 402 - 5834.

Sincerely,

{See appended electronic signature page}

Jennifer Swisher, Ph.D., Review Chief
Division of Biotechnology Review and
Research IV
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Enclosure: Written Responses

WRITTEN RESPONSES

Meeting Type: Biosimilar Biological Product Development

Meeting Category: BPD Type 2 WRO

Application Number: IND 146085

Product Name: CT-P43

Indication: CT-P43 is being developed for the same indications as approved for US-licensed Stelara

Sponsor Name: Celltrion, Inc.

Regulatory Pathway: 351(k) of the Public Health Service Act

1.0 BACKGROUND

CT-P43 is currently under global development and has not been submitted for marketing authorization/licensure in any region, nor is marketed anywhere in the world. CT-P43 is intended to be submitted to the FDA under a 351(k) BLA application as proposed biosimilar to US-licensed Stelara.

The primary purpose of the meeting is to obtain the FDA's advice on the selection of an IL-12 reporter assay for use as the potency assay.

FDA may provide further clarifications of, or refinements and/or changes to these written responses based on further information provided by Celltrion, Inc., and as the FDA'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:

CELLTRION has conducted a study using stressed samples to determine if the hIL-12 reporter assay is an appropriate cell-based bioassay for use as potency assay in place of the (b) (4) Based on the provided information, does the FDA agree that the IL-12 reporter assay is suitable for use as the potency assay in release testing and stability studies?

FDA Response to Question 1:

Yes, we agree that the IL-12 reporter assay appears to be suitable for use in release and stability testing for CT-P43. To facilitate review, submit the method validation data and method comparability data in the BLA submission.

APPEARS THIS WAY ON ORIGINAL

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/

KRISTINE F LEAHY
04/25/2022 05:25:21 PM

JENNIFER F SWISHER
04/25/2022 05:30:22 PM



IND 146085

MEETING MINUTES

CELLTRION, Inc.
c/o Parexel International
Attention: Ally Danta
Senior Associate, Regulatory
2520 Meridian Parkway, Suite 200
Durham, NC 27713

Dear Ms. Danta:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CT-P43.

We also refer to the teleconference between representatives of your firm and the FDA on December 13, 2021. The purpose of the meeting was to discuss the development program for CT-P43.

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

If you have any questions, call Qianyiren Song, Regulatory Project Manager at 301-796-2581.

Sincerely,

{See appended electronic signature page}

Shari L. Targum, MD, MPH, FACP, FACC
Deputy Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor's response to the Agency's preliminary comments
- Slide Presentation

MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: BPD Type 2

Meeting Date and Time: December 13, 2021; 1:30 – 2:30 p.m. EST
Meeting Location: Teleconference

Application Number: IND 146085
Product Name: CT-P43

Proposed Indication: CT-P43 is being developed for the same indications as those approved for US-licensed Stelara (ustekinumab)

Sponsor: Celltrion, Inc.
Regulatory Pathway: 351(k) of the Public Health Service Act

Meeting Chair: Shari L. Targum, MD
Meeting Recorder: Qianyiren Song, PharmD

FDA ATTENDEES

Shari L. Targum, MD, MPH, FACP, FACC, Deputy Director, Division of Dermatology and Dentistry (DDD)
Amy Weitach, OD, Clinical Team Leader, DDD
Maryjoy Meija, MD, Clinical Reviewer, DDD
Stacey Ricci, M. Eng, ScD, Director, Scientific Review Staff (SRS), Office of Therapeutic Biologics and Biosimilars (OTBB)
Nina Brahme, PhD, MPH, Scientific Reviewer, SRS, OTBB
Thomas Herndon, MD, Scientific Reviewer, SRS, OTBB
Carol Kim, PharmD, Scientific Reviewer, SRS, OTBB
Sarah Brown, PharmD, Science Policy Analyst, SRS, OTBB
Emily Gebbia, JD, Director, Policy Staff, OTBB
Shelley Skibinski, Pharm.D., Project Coordinator, Policy Staff, OTBB
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DCP) 3
Da Zhang, PhD, Clinical Pharmacology Reviewer, DCP3
Mohamed Alish, PhD, Biometrics Team Leader, Division of Biometrics III (DB III)
Kathleen Fritsch, PhD, Biometrics Reviewer, DB III
Murewa Oguntimein, PhD, Human Factors Team Lead (Acting), Division of Medication Error Prevention & Analysis (DMEPA)
Neha Kumar, PharmD, Safety Evaluator, DMEPA
Chana Fuchs, PhD, Team Leader, Office of Biotechnology Products
Tri Bui-Nguyen, PhD, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)

Margaret Kober, Acting Chief, Project Management Staff, Division of Regulatory Operations for Dermatology and Dentistry (DRO – DD)

Qianyiren “Cicy” Song, PharmD, Regulatory Project Manager, DRO-DD

SPONSOR ATTENDEES

Keith Watson, Vice President of Regulatory Affairs Division, Celltrion

Minkyung Jeon, Head of Regulatory Affairs Department, Celltrion

Jonghwan Kim, Head of Clinical Regulatory Affairs Department, Celltrion

Bianca Park, Team leader of Clinical Regulatory Affairs, Celltrion

Suwon Song, Team leader of Regulatory Affairs, Celltrion

Shinmyum Park, Manager of Regulatory Affairs, Celltrion

Hyojin Kim, Assistant Manager of Clinical Regulatory Affairs, Celltrion

Seungyeon Huh, Assistant Manager of Regulatory Affairs, Celltrion

(b) (4)

1.0 BACKGROUND

Purpose of meeting:

The purpose of the meeting is to discuss the proposed development for CT-P43, as a biosimilar to US-licensed Stelara.

FDA may provide further clarifications of, or refinements and/or changes to the responses and the advice provided at the meeting based on further information provided by CELLTRION, Inc. 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

Global Comment:

(b) (4)

Meeting Discussion:

(b) (4)

2.1. Clinical**Question 1:**

CELLTRION plans to publish Clinical Study Report (CSR) for Study CT-P43 3.1 up to Week 28 with an equivalence margin of [-15%, +15%] using 95% confidence interval (CI) for the primary efficacy endpoint, the equivalence margin for global submission. For US BLA, CELLTRION intends to submit the CSR but include the efficacy data in CTD sections including Section 2.5 (Clinical Overview) and Section 2.7.3 (Summary of Clinical Efficacy) analyzed with a margin of [-10%, +10%] using 90% CI in line with the discussion with the FDA. Does the FDA agree that the proposed analysis approach is appropriate to support BLA?

FDA Response to Question 1:

Clarify whether different protocol versions were used at different sites or countries. The most recent protocol version submitted to the IND on August 24, 2021, does not indicate that alternate analysis plans are planned for different regulatory authority submissions. If different protocol versions were used at different sites, clarify whether there were any differences in inclusion/exclusion criteria, assessment scales or timing of assessments, or any other aspect of the protocol besides the statistical analysis plan among the versions in use. If multiple versions of the protocol were used to collect data for Study CT-P43 3.1, the Clinical Study Report (CSR) should address all of the final analysis plans that are planned for submission to regulatory authorities. We do not agree that the CSR can include only the analyses intended for the 'global' submissions, with the analyses intended for US regulatory submissions only included in the Clinical Overview and Summary of Clinical Efficacy.

In particular, the CSR should include the analyses agreed upon by FDA and the sponsor as previously conveyed in the Special Protocol Assessment-No Agreement (June 3, 2020) and Study May Proceed (December 16, 2020) letters. These include your proposal to estimate the treatment difference and its 90% confidence interval (CI) for the primary efficacy endpoint using analysis of covariance (ANCOVA) with treatment, baseline Psoriasis Area and Severity Index (PASI) score, and the factors used to stratify the randomization as factors in the model, equivalence margins of $\pm 10\%$, and an analysis population based on all randomized subjects dispensed study product regardless of weight category and whether the subjects undergo any post-baseline assessments (i.e., all subjects who were dispensed treatment, even if they did not inject at least one full dose of study drug should be included in the analysis).

Question 2:

CELLTRION is planning to seek licensure of CT-P43 45 mg/0.5 mL and 90 mg/1 mL in
(b) (4) a pre-filled syringe with safety guard (PFS). To

(b) (4)

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

Please be advised that an original 351(k) BLA will be subject to “the Program” under BsUFA II. Therefore, at an appropriate time, you should request a BPD Type 4 (pre-351(k) BLA) meeting and 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.

Include in your BPD Type 4 meeting package your proposals for 1) the content of a complete application and 2) any minor components to be submitted within 30 days after your original submission. You should also include, as part of your meeting questions, a request for our agreement with your proposals.

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

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities. Information on the Program is available at FDA.gov.⁴

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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 additional information on how you may fulfill the requirement for pediatric assessments or investigations under PREA, see question and answer I.16 in the guidance for industry, *Questions and Answers on Biosimilar Development and the BPCI Act*.

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*⁵. 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.

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⁶ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cdereadata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁷ that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.⁸

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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⁸ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

⁹ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

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<https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>

¹¹ <http://www.fda.gov/ectd>

specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.¹²

4.0 ATTACHMENTS

- **Sponsor Agenda**
- **Slide Presentation**

¹² <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

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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IND 146085

MEETING PRELIMINARY COMMENTS

Celltrion, Inc.
C/o: Parexel International
Attention: Riley Jones, PhD
Consultant, Regulatory Affairs
2520 Meridian Pkway, #200
Durham, NC 27713

Dear Dr. Jones:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CT-P43.

We also refer to your March 21, 2021, correspondence, received March 21, 2021, requesting a meeting to discuss the development program for CT-P43.

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)796-5376.

Sincerely,

{See appended electronic signature page}

Dawn Williams, BSN
Safety Regulatory Project Manager
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

IND 146085

Page 2

ENCLOSURE:

Preliminary Meeting Comments



PRELIMINARY MEETING COMMENTS

Meeting Type: Biosimilar
Meeting Category: BPD Type 2
Meeting Date and Time: June 23, 9:30-10:30am
Meeting Format: Teleconference
Application Number: IND 146085
Product Name: CT-P43
Proposed Indication: CT-P43 is being developed for the same indications as approved for US-licensed Stelara
Sponsor Name: Celltrion, Inc.
Regulatory Pathway: 351(k) of the Public Health Service Act

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for June 23, 2021; 9:30-10:30am between Celltrion, Inc. and the Division of Dermatology and Dentistry. 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. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the 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.

Coronavirus-19 (COVID-19) Clinical Trial Guidance:

During the COVID-19 public health emergency, ensuring the safety of study participants is paramount. Sponsors should consider each circumstance, focus on the potential impact on the safety of study participants, and modify study conduct accordingly. It is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them, and that the Agency is appropriately informed of these changes. Refer to the *FDA Guidance on [Conduct of Clinical Trials of Medical Products](#)*

during COVID-19 Public Health Emergency (March 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

1.0 BACKGROUND

Regulatory Correspondence History:

We have had the following meetings/teleconference with you:

- 9/23/2020 Biosimilar Biological Product Development (BPD) Type 2
- 2/26/2020 Biosimilar Biological Product Development (BPD) Type 2

We have sent the following correspondences:

- 3/17/2021 Human Factors Advice
- 12/16/2020 Study May Proceed
- 10/30/2020 Advice
- 10/28/2020 Advice (2)
- 6/3/2020 Special Protocol- No Agreement

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 Celltrion, Inc. 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

2.1. Chemistry, Manufacturing, and Controls

(b) (4)

2.2. Clinical

Question 4:

Does the Agency agree with the proposed method for handling missing data for primary efficacy endpoint of Study CT-P43 3.1?

FDA Response to Question 4:

No. We do not agree with your proposal to use a complete case analysis for the primary analysis. While we agree that when the amount of missing data is small, missing data will have only a limited impact on the conclusions, we also think it is important to use an appropriate imputation method for the primary analysis, as the assumptions underlying a complete case analysis are not likely to be satisfied. While all methods of handling missing data have limitations and drawbacks, we recommend using a multiple imputation approach as the primary method of handling missing data with supportive analyses that use alternate assumptions and a tipping point analysis. To ensure that these analyses are fully prespecified, we recommend including complete details regarding these methods in the protocol/statistical analysis plan.

In addition, as we noted in the Special Protocol Assessment – No Agreement Letter dated 6/3/2020, we recommend defining the Full Analysis Set (FAS) as all randomized subjects dispensed study product regardless of whether the subjects have any post-baseline assessments. Thus, we recommend including all subjects

who were dispensed treatment, even if they did not inject at least one full dose of study drug.

Question 5:

CELLTRION plans to develop CT-P43 PFS in higher dose (90 mg SC PFS) without conducting a bioequivalence study between the CT-P43 45 mg SC PFS and 90 mg SC PFS. Does the Agency concur with the approach?

FDA Response to Question 5:

If PK similarity is established with 45 mg SC dose, an additional PK comparability study between the CT-P43 45 mg/0.5 mL PFS and CT-P43 90 mg/mL PFS is not necessary. Also a PK similarity study with the IV formulation is not necessary.

Additional comments:

1. You indicate that the target fill volume of the CT-P43 presentations will be based on (b) (4) as indicated in section 13.1.4. The fill volume for your product should be based on your assessment of the deliverable/extractable volume data generated for CT-P43, capability for the commercial CT-P43 drug product manufacturing including (fill weight, process variability, etc), CT-P43 container closure considerations (e.g. hold up volume). Fill volume should be consistent with USP <1151> guidelines for vial presentations and should be supported by extractable/deliverable experimental data.
2. Regarding your plan for the comparative stability and forced degradation studies to support a demonstration that CT-P43 is highly similar to US-licensed Stelara and to establish the analytical portion of the scientific bridge, we have the following recommendations:
 - a. Provide a justification for the attributes that will be evaluated. The comparative stability studies should include an evaluation of rate of degradation and type of degradation species.
 - b. The stress conditions that will be used in the forced degradation studies are not clear. Provide a scientific justification for the stress conditions used in the forced degradation studies. You should select stress conditions that are relevant to your product.

Refer to the draft guidance for industry *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations* (May 2019), ICH Q1A, and ICH Q5C for additional guidance.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

Please be advised that an original 351(k) BLA will be subject to “the Program” under BsUFA II. Therefore, at an appropriate time, you should request a BPD Type 4 (pre-351(k) BLA) meeting and 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.

Include in your BPD Type 4 meeting package your proposals for 1) the content of a complete application and 2) any minor components to be submitted within 30 days after your original submission. You should also include, as part of your meeting questions, a request for our agreement with your proposals.

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

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

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

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 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

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

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*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.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.³

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

³ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cdeleredata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁴ that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at www.fda.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

⁴ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.⁵

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/s/

DAWN WILLIAMS
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