

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125544Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 125544 Supplement Number: \_\_\_\_\_ NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: DPARP PDUFA Goal Date: 6/8/2015 Stamp Date: 8/8/2014

Proprietary Name: Inflectra

Established/Generic Name: CT-P13

Dosage Form: intravenous infusion

Applicant/Sponsor: Celltrion

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):      
(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** Crohn's Disease (CD), Pediatric Crohn's Disease, Ulcerative Colitis (UC), Pediatric Ulcerative Colitis, Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), and Plaque Psoriasis (Ps)

**Q1:** Is this application in response to a PREA PMR? Yes  Continue  
No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_ Supplement #: \_\_\_\_\_ PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q4:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
  - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

*Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).*

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

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pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Population	minimum	maximum	Ready for Approval in Adults
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.

\* Other Reason: Deferral is being requested for pediatric UC until the expiration of orphan exclusivity on September 23, 2018

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?       No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?       No;  Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

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*If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.*

This page was completed by:

*{See appended electronic signature page}*

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Regulatory Project Manager

(Revised: 6/2008)

**NOTE: If you have no other indications for this application, you may delete the attachments from this document.**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** \_\_\_\_\_**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

**Q2:** Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - Deferred for some or all pediatric subpopulations (Complete Sections C)
  - Completed for some or all pediatric subpopulations (Complete Sections D)
  - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.*

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

**#** Not feasible:

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\*** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**†** Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ** Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

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proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

**Section C: Deferred Studies (for some or all pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.*

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.*

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.***

This page was completed by:

*{See appended electronic signature page}*

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 6/2008)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PHUONG N TON  
04/23/2015

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # BLA # 125544	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Inflectra Established/Proper Name: infliximab-dyyb Dosage Form: 100 mg of lyophilized infliximab-dyyb for intravenous infusion		Applicant: Celltrion, Inc. Agent for Applicant (if applicable): Parexel International
RPM: Nina Ton		Division: DPARP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input checked="" type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b> <ul style="list-style-type: none"> <li><input type="checkbox"/> No changes</li> <li><input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i></li> </ul> </li> </ul> <p>Date of check: _____</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>April 5, 2016</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input type="checkbox"/> None CR 6/8/2015
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type Remicade's indication for pediatric Ulcerative Colitis is protected by orphan drug exclusivity expiring on September 23, 2018.	<input type="checkbox"/> No <input checked="" type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) AP 4/5/2016 CR 6/8/2015
Labeling	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> </ul>	11/24/2015, 2/23/2015, 2/17/2015, 10/28/2014
<ul style="list-style-type: none"> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul>	11/20/2015, 2/23/2015, 10/28/2014
❖ Labeling reviews ( <i>indicate dates of reviews</i> )	RPM: <input type="checkbox"/> None 9/19/2014 DMEPA: <input type="checkbox"/> None 4/4/2016, 3/30/2016, 3/8/2016, 5/4/2015 DMPP/PLT (DRISK): <input type="checkbox"/> None 4/1/2016, 5/27/2015 OPDP: <input type="checkbox"/> None 4/4/2016, 6/10/2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input type="checkbox"/> None 4/4/2016, 3/29/2016, 5/19/2015 Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting ( <i>indicate date of each review</i> )	10/21/2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC 2/24/2016, 4/29/2015 If PeRC review not necessary, explain: _____</li> </ul>	3/18/2016, 5/27/2015, 5/14/2015
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) ( <i>do not include previous action letters, as these are located elsewhere in package</i> )	4/1/2016, 3/30/2016, 3/18/2016 (2), 3/11/2016, 3/9/2016, 2/4/2016, 1/12/2016, 1/4/2016, 10/14/2015, 9/25/2015, 9/10/2015, 8/4/2015, 7/1/2015, 5/27/2015, 5/6/2015, 4/10/2015, 4/7/2015, 4/1/2015, 3/20/2015, 2/27/2015, 2/13/2015, 2/10/2015, 2/6/2015, 2/5/2015 (2), 2/4/2015, 1/29/2015, 1/14/2015, 1/13/2015, 12/22/2014, 12/16/2014, 12/10/2014 (2), 11/26/2014, 11/20/2014, 11/14/2014, 11/5/2014, 10/21/2014 (2), 10/16/2014, 10/7/2014, 10/1/2014, 9/26/2014, 9/23/2014, 8/20/2014
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	12/30/2014
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 4/28/2014
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) BPD Type 1</li> </ul>	8/5/2015
❖ Advisory Committee Meeting(s)	<input type="checkbox"/>
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	2/9/2016
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/5/2016
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/5/2016
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews	

<ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>• Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	3/11/2016, 5/4/2015, 10/8/2014
<ul style="list-style-type: none"> <li>• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	5/21/2015
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None 4/5/2016 (DGIEP) 4/4/2016 (DDDP)
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested 11/9/2015, 6/18/2015, 6/3/2015, 5/26/2015, 5/20/2015 (2), 5/7/2015
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3/10/2016, 5/4/2015 (CMC Stats) 5/4/2015, 10/7/2014 (Clin Stats)
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3/11/2016, 5/4/2015, 10/7/2014
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input type="checkbox"/> None requested 5/22/2015, 2/23/2015

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review 5/8/2015
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3/28/2016, 5/4/2015, 9/22/2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3/10/2016, 5/11/2015
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 3/10/2016, 3/8/2016, 1/7/2016, 1/5/2016, 5/7/2015, 9/30/2014
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input type="checkbox"/> None 2/1/2016, 5/22/2015, 5/8/2015 (Immunogenicity) 2/24/2016 (Micro DP), 5/14/2015 (Micro DS), 5/7/2015 (Micro DP), 10/1/2014 (Micro DP)
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	Page 8 of CMC review dated 5/7/2015
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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/s/  
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PHUONG N TON  
04/05/2016



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

---

**Date:** April 1, 2016

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, PharmD Senior Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 Inflectra Labeling Comments

Total no. of pages including  
cover and signature page 65

**Comments:** Please acknowledge receipt and respond by 9:00 AM Monday,  
April 4, 2016

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Document to be emailed to: [Sally.Choe@parexel.com](mailto:Sally.Choe@parexel.com)

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BLA 125544  
Inflectra  
Celltrion, Inc.

Dear Dr. Choe:

We are currently reviewing your BLA submitted on October 5, 2015, and your proposed labeling submitted on March 24, 2016. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Please be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

We also have the following comments regarding your revised container label and carton labeling.

(b) (4) Vial Cap

In your February 23, 2016, submission, you propose to release three batches of drug product that contain (b) (4) text on the vial caps. Additionally, all future drug product batches will not contain text on the (b) (4) flip caps. We find your proposal acceptable.

Container Label and Carton Labeling

Revise (b) (4) to "Single-use vial".

In order to facilitate the review of your submission, provide the requested information no later than 9:00 AM Monday, April 4, 2016. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

BLA 125544  
Inflectra  
Celltrion, Inc.

Drafted by: NTon/March 30, 2016  
Cleared by: SBarnes/March 30, 2016  
              SYim/April 1, 2016  
Finalized by: NTon/April 1, 2016

62 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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PHUONG N TON  
04/01/2016



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

---

**Date:** March 30, 2016

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, PharmD Senior Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 Inflectra Labeling Comments

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Total no. of pages including  
cover and signature page      68

**Comments:** Please acknowledge receipt and respond by 12:00 PM Friday,  
April 1, 2016

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Document to be emailed to: [Sally.Choe@parexel.com](mailto:Sally.Choe@parexel.com)

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copying, or other action based on the content of this communication is not  
authorized. If you have received this document in error, please notify us  
immediately by telephone at (301) 796-2300. Thank you.**

BLA 125544  
Inflectra  
Celltrion, Inc.

Dear Dr. Choe:

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In order to facilitate the review of your submission, provide the requested information no later than 12:00 PM Friday, April 1, 2016. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

BLA 125544  
Inflectra  
Celltrion, Inc.

Drafted by: NTon/March 30, 2016  
Cleared by: SYim/March 30, 2016  
SBarnes/March 30, 2016  
Finalized by: NTon/March 30, 2016

65 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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PHUONG N TON  
03/30/2016



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** March 18, 2016

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, PharmD Senior Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 Inflectra Labeling Comments

Total no. of pages including  
cover and signature page 82

**Comments:** Please acknowledge receipt and respond by March 23, 2016

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Document to be emailed to: [Sally.Choe@parexel.com](mailto:Sally.Choe@parexel.com)

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BLA 125544  
CT-P13  
Celltrion, Inc.

Dear Dr. Choe:

We are currently reviewing your BLA submitted on October 5, 2015, and your proposed labeling submitted on November 14, 2014. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Please be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

In order to facilitate the review of your submission, provide the requested information no later than March 23, 2016. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/March 18, 2016  
Cleared by: LJafari/March 18, 2016  
NNikolov/March 18, 2016  
Finalized by: NTon/March 18, 2016

79 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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PHUONG N TON  
03/18/2016



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** March 18, 2016

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, PharmD Senior Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648
<b>Subject:</b> BLA 125544 Inflectra Container Label and Carton Labeling Comments	
Total no. of pages including cover and signature page 5	
<b>Comments:</b> Please acknowledge receipt and respond by March 22, 2016	

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Document to be emailed to: [Sally.Choe@parexel.com](mailto:Sally.Choe@parexel.com)

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Dear Dr. Choe:

We are reviewing your submission dated October 5, 2015, and we have the following comments regarding your revised container label and carton labeling submitted on February 23, 2016. Please be advised that these changes are not necessarily the Agency's final recommendations and that additional changes may be forthcoming as the container and carton label are continued to be reviewed.

**1. Carton Labeling, 10-count and 1-count**

- a. Revise "Single-use vial" to "Single-dose vial."
- b. Revise the "Dispense the enclosed Medication Guide to each patient. [REDACTED] (b) (4) [REDACTED]" statement to the following to reduce clutter on the Principal Display Panel:

Dispense the enclosed Medication Guide to each patient.

- c. Revise and bold the storage statement to the following to increase the prominence of this important information and to minimize the risk of the storage information being overlooked:

Store in refrigerator at 2°C - 8°C (36°F - 46°F).

- d. If listing a distributor (Hospira, a Pfizer Company), add the distributor address to comply with 21 CFR 610.64.

- e. [REDACTED] (b) (4) [REDACTED] Revise the manufacturer information so that the license number appears with the licensed manufacturer. For example:

Manufactured by:  
Celltrion, Inc.  
23, Academy-ro  
Yeonsu-gu, Incheon,  
406-840, Republic of Korea  
US License No. 1996

for  
Hospira, a Pfizer Company  
[insert distributor address]

- f. Consider utilizing the additional space on the side panel that currently contains the barcode to improve the spacing and reduce the cluttered appearance. Consider the following:

- i. Relocate the storage information from the bottom of the cluttered side panel to the top of the side panel that contains the manufacturer information and barcode.
  - ii. Relocate the “No U.S. standard of potency” to side panel that contains the manufacturer information and barcode.
- g. If space permits after making the above recommendations, consider adding some (b) (4) space between the dosage form, strength, and route of administration. For example:

Inflectra  
(infliximab-dyyb)  
for Injection  
100 mg per vial  
For Intravenous Infusion Only

## 2. Carton Labeling, 1-count

- a. Place the “Rx Only” statement after the “Infuse over at least 2 hours with an in-line filter” statement on the PDP to comply with 21 CFR 610.61(s).

## 3. Vial Container Label

- a. Revise “Single-use vial” to “Single-dose vial.”
- b. We consider the Vial Container Label a partial label due to its small size, per 21 CFR 610.60(c). Our recommendations below are intended to preserve the required and recommended information on the label and remove less important information to provide more white space and improve readability.
  - i. Removing bolding of manufacturer information.
  - ii. Delete (b) (4).
  - iii. Delete (b) (4) so that the manufacturer information reads:  
Mfd by: Celltrion, Inc.
- c. Bold storage information.
- d. Add a linear barcode. We requested this in the February 4, 2016, labeling comments; however, your February 23, 2016, submission did not address this request.

## 4. (b) (4) Cap

Your February 23, 2016, response notes the wording (b) (4). Please clarify if (b) (4) cap.

BLA 125544  
Inflectra  
Celltrion, Inc.

In order to facilitate the review of your submission, provide the requested information no later than March 22, 2016. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

BLA 125544  
Inflectra  
Celltrion, Inc.

Drafted by: JAbdus-Samad/March 17, 2016  
NTon/March 18, 2016

Cleared by: LJafari/March 18, 2016  
JAbdus-Samad/March 18, 2016  
NNikolov/March 18, 2016  
TBBS/March 18, 2016

Finalized by: NTON/March 18, 2016

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/s/  
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PHUONG N TON  
03/18/2016

**PeRC Meeting Minutes  
February 24, 2016**

**PeRC Members Attending:**

Lynne Yao

Ikram Elayan

Kevin Krudys

Gettie Audain

Daiva Shetty

Meshaun Payne

Gerri Baer

Wiley Chambers

Julia Pinto

Maura O'Leary

(b) (4)

Lili Mulugeta

Peter Starke

Ruthanna Davi

Raquel Tapia

Greg Reaman

Dionna Green

Barbara Buch

Rachel Witten

Michelle Roth-Kline

George Greeley

**Agenda**

NON-RESPONSIVE

11:20	BLA 125544	Inflectra (CT-P13) Biosimilar to Remicade (infliximab) Partial Waiver Deferral/Plan (with Agreed iPSP)	DPARP	Nina Ton	Approved indication of Remicade such as Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Pediatric Ulcerative Colitis, Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis
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NON-RESPONSIVE

**Inflectra (CT-P13) Biosimilar to Remicade (infliximab) Partial Waiver Deferral/Plan (with Agreed iPSP)**

- Proposed Indication: Approved indication of Remicade such as Crohn’s Disease, Pediatric Crohn’s Disease, Ulcerative Colitis, Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis
- The product triggers PREA as a new indication and has a PDUFA Goal date of April 5, 2016.
- The division provided the plan for assessments as follows:
  - Juvenile Idiopathic Arthritis (JIA)
    - < 4 Partial Waiver
    - 4 to 17 Pediatric assessment complete based on extrapolation of pediatric information from the reference product
  - Ankylosing Spondylitis (AS)
    - 0 to 17 Full Waiver
  - Crohn’s Disease (CD)
    - < 6 Partial Waiver
    - 6 to 17 Pediatric assessment complete based on extrapolation of pediatric information from the reference product

(b) (4)

Psoriatic Arthritis (PsA)

- 0 to 17 Full Waiver

Plaque Psoriasis (PsO)

- 0 to 17 Full Waiver

- *PeRC Recommendations:*

- The PeRC agreed with the division's plan for assessments for each indication and age group stated in the Agreed iPSP.

NON-RESPONSIVE

1 Page(s) has been Withheld in Full as NON-RESPONSIVE immediately following this page

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GETTIE AUDAIN  
03/18/2016



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** March 11, 2016

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Senior Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 Information Request

Total no. of pages including  
cover and signature page 3

**Comments:** Please acknowledge receipt and respond by March 18, 2016

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Document to be emailed to: Sally.Choel@parexel.com

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BLA 125544  
CT-P13  
Celltrion, Inc.

Dear Dr. Choe:

We are reviewing your submission dated October 5, 2015, and have the following request for information.

Submit an amendment to your 351(k) BLA to include information found in the “action package” for the Remicade BLA efficacy supplement (BLA 103772, Supplement 5113) approved on September 15, 2005, (see draft guidance on Biosimilars: Additional Questions and Answers Regarding Implementation of the BPCI Act, Q+A I.13). For your convenience, your amendment may provide a Web link to the Summary Basis of Approval and FDA reviews currently available at [Drugs@FDA](mailto:Drugs@FDA), accompanied by a list of the documents that you intend to reference (identified by title and date), and this information will be incorporated by reference into your 351(k) BLA.

In order to facilitate the review of your submission, provide the requested information no later than March 18, 2016.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/March 9, 2016  
Cleared by: LJafari/March 9, 2016  
              TBBS/March 10, 2016  
              JWeiner/March 10, 2016  
              NNikolov/March 10, 2016  
Finalized by: NTon/March 11, 2016

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/s/  
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PHUONG N TON  
03/11/2016



BLA 125544

## GENERAL ADVICE

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

Attention: Sally Choe, PhD  
Senior Director, Parexel International

Dear Dr. Choe:

Please refer to your Biologics License Application (BLA) submitted under section 351(k) of the Public Health Service Act for CT-P13.

We also refer to your November 17, 2015, submission, containing your request for review of the proposed suffixes for the nonproprietary name of your product.

We have reviewed the referenced material and have the following comments:

We find the nonproprietary name, infliximab-dyyb acceptable for your proposed product. Revise your proposed labels and labeling accordingly. The nonproprietary name containing the distinguishing suffix will be the proper name designated in the license should your 351(k) BLA be approved.

FDA's comments on the nonproprietary name for this product do not constitute or reflect a decision on a general naming policy for biosimilar products. FDA issued draft guidance on Nonproprietary Naming of Biological Products in August 2015, and the Agency is carefully considering the comments submitted to the public docket as we move forward in finalizing the draft guidance. As result, the nonproprietary name is subject to change to the extent that it is inconsistent with any general naming policy for biosimilar products established by FDA. Were the name to change, we would work with you to minimize the impact this would have to your manufacture and distribution of this product, should it be licensed.

If you have any questions, call Nina Ton, Senior Regulatory Project Manager, at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, MD, PhD  
Director  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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BADRUL A CHOWDHURY  
03/09/2016



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** February 4, 2016

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, PharmD Senior Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 Container and Carton Labeling Comments

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**Comments:** Please acknowledge receipt and respond by February 22, 2016

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Dear Dr. Choe:

We are reviewing your submission dated October 5, 2015, and we have the following comments regarding your proposed container label and carton labeling submitted on August 8, 2014. Please note that within the following container label and carton labeling comments, we refer to Celltrion's proposed product using the descriptor "CT-P13\*" in place of the nonproprietary name because the nonproprietary name for Inflectra has not yet been determined. "CT-P13\*" is not intended to be included on your final printed labels or labeling. Also, please be advised that additional comments on your container label and carton labeling will be forthcoming upon the Agency's determination of the nonproprietary name and as we continue to review your submissions.

### 1. General Comments

- a. Replace all instances of the proprietary name "(b) (4)" with "Inflectra" on the container label and carton labeling.
- b. Confirm there is (b) (4) cap over seal of the vials to comply with a revised United States Pharmacopeia (USP), General Chapters: <1> Injections, Packaging, Labeling on Ferrules and Cap Overseals.
- c. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

### 2. Carton Labeling, 10 vials

- a. Add the NDC to the top one-third portion of the carton labeling to comply with 21 CFR 201.2.
- b. Ensure the font size of "CT-P13\*" is at least half the font size of the proprietary name "Inflectra" per 21 CFR 201.10.
- c. Revise the strength statement "(b) (4)" that appears in the green (b) (4) to read "100 mg per vial" or "100 mg/vial"<sup>1</sup>.
- d. Relocate the strength statement "100 mg per vial" from alongside the dosage form, for Injection, to appear below the dosage form.

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\* FDA is using the descriptor "CT-P13\*" in place of the nonproprietary name because the nonproprietary name for Inflectra has not been determined. CT-P13 is not intended to be included in your final printed labels and labeling.

<sup>1</sup> FDA draft Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*. April 2013.

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

- e. Add the route of administration “For Intravenous Infusion Only” to appear below the strength. For example:

Inflectra  
(b) (4)  
for Injection  
100 mg per vial  
For Intravenous Infusion Only

- f. Revise the statement (b) (4) to “Reconstitute and Dilute Before Intravenous Infusion.”
- g. Revise the statement (b) (4) to “Infuse over at least 2 hours with an in-line filter.”
- h. Revise the medication guide to read “Dispense the enclosed Medication Guide to each patient.”
- i. Revise the reconstitution and dilution instructions on the side panel to read as follows:

Reconstitute each vial with 10 mL Sterile Water for Injection, USP. The resulting concentration is 10 mg/mL. Do NOT shake reconstituted solution. Further dilute with 0.9% Sodium Chloride Injection, USP. See insert for full preparation instructions.

- j. Revise the manufacturer information to comply with per 21 CFR 600.3(t) and 21 CFR 610.61(b). The manufacturer is the “Applicant” or licensee that appears on your submitted 356h form. For example:

“Manufactured by:” (Licensee or Applicant on the 356h form)  
Celltrion, Inc.  
23, Academy-ro  
Yeonsu-gu, Incheon, 406-840, Republic of Korea  
US License No. 1996

- k. Add a linear bar coder to comply with 21 CFR 610.67.
- l. Ensure the carton labeling and prescribing information list all the inactive ingredients. Currently, the list of inactive ingredients and their respective amounts in both the proposed prescribing information and carton labeling differ. Additionally, revise the list of ingredients to comply with 21 CFR 201.100(b)(iii) and USP General Chapters: <1091> Labeling of Inactive Ingredients, by listing the names of the inactive ingredients in alphabetical order in the following format: inactive ingredient (amount). For example:

Once reconstituted, each mL contains (b) (4) 10 mg, di-sodium hydrogen phosphate dihydrate (x mg), polysorbate 80 (x mg), sodium dihydrogen phosphate monohydrate (x mg), and sucrose (x mg).

### 3. Carton Labeling, 1 vial

- a. See comments 2b, 2e, 2f, 2g, 2h, 2i, 2j, 2k, and 2l.
- b. Remove the (b) (4) from (b) (4). The (b) (4) are competing with important information.<sup>1</sup>

### 4. Vial Container Label

- a. See comments 2b, 2e, and 3b.
- b. We consider the Vial Container Label a partial label due to its small size, per 21 CFR 610.60(c). Our recommendations below are intended to preserve the required and recommended information on the label and remove less important information to provide more white space and improve readability.
  - i. Revise the presentation of the NDC, proprietary name, nonproprietary name, dosage form, and strength on the PDP from vertical to horizontal orientation so the text on the label is oriented in the same direction.<sup>1</sup>
  - ii. Increase the prominence of the strength “100 mg per vial” by bolding or increasing the font size.
  - iii. Revise the statement (b) (4) to “Reconstitute and Dilute Before Intravenous Infusion.”
  - iv. Delete the statement, (b) (4)
  - v. Revise the statement “(b) (4)” to read “See insert.”
  - vi. Revise the manufacturer information to read:  
Mfd by: Celltrion, Inc.  
(b) (4)
  - vii. Delete (b) (4)
- c. If there is space on the label, add a linear barcode (b) (4).  
(b) (4)

BLA 125544  
CT-P13  
Celltrion, Inc.

In order to facilitate the review of your submission, provide the requested information no later than February 22, 2016. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/February 1, 2016  
Cleared by: LJafari/February 1, 2016  
NNikolov/February 1, 2016  
JAbdus-Samad/February 2 and 4, 2016  
TBBS/February 4, 2016  
Finalized by: NTon/February 4, 2016

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/s/  
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PHUONG N TON  
02/04/2016



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** January 12, 2016

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Senior Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 Information Request

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**Comments:** Please acknowledge receipt and respond by January 19, 2016

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Document to be emailed to: Sally.Choe@parexel.com

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BLA 125544  
CT-P13  
Celltrion, Inc.

Dear Dr. Choe:

We are reviewing your submission dated October 5, 2015, and have the following requests for information. These requests pertain to the [REDACTED] (b) (4) [REDACTED].

1. Module 3.2.P.3.5.15 Shipping Validation. You indicate that unlabeled drug product will be shipped to [REDACTED] (b) (4). Provide the address and FEI number where Primary Labeling and Secondary Packaging (Labeling and Cartonning) will be conducted, and include the inspection history for the facility.
2. Update your 356h form for [REDACTED] (b) (4) to include the FEI number and the address where Primary Labeling and Secondary Packaging will be conducted (Labeling and Cartonning).

In order to facilitate the review of your submission, provide the requested information no later than January 19, 2016. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/January 11, 2016  
Cleared by: WSeifert (DIA/OPQ)/January 11 and 12, 2016  
LJafari/January 11, 2016  
TBBS/January 12, 2016  
Finalized by: NTon/January 12, 2016

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/s/  
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PHUONG N TON  
01/12/2016



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** January 4, 2016

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Senior Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 CMC Information Request

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**Comments:** Please acknowledge receipt and respond by January 8, 2016

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BLA 125544  
CT-P13  
Celltrion, Inc.

Dear Dr. Choe:

We are reviewing your submission dated October 5, 2015, and have the following request for information:

We have concerns regarding your control strategy in which you propose a drug substance (DS) acceptance criterion for Fc $\gamma$ RIIIa V type of (b) (4) % (% relative potency). This value is based on mean values +/- 3SD generated from the analysis of CT-P13 lots that were assessed alongside US-licensed Remicade for NK ADCC activity. Further, your proposed acceptance criterion does not contain an upper bound. Develop a tighter control strategy, which includes an upper and lower bound, for Fc $\gamma$ RIIIa binding for the drug substance such that the release specifications assure that the CT-P13 product is appropriately controlled within the variability of the reference product (e.g., within 3 SD of the reference product mean).

In order to facilitate the review of your submission, provide the requested information no later than January 8, 2016. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/December 23, 2015  
Cleared by: KBrorson/December 23 and 28, 2015  
DFrucht/December 28, 2015  
SKozlowski/December 28, 2015  
LJafari/December 23, 2015  
TBBS/December 24 and 31, 2015  
Finalized by: NTon/January 4, 2016

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/s/  
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PHUONG N TON  
01/04/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

BLA 125544

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Sally Choe, PhD  
Senior Director

Dear Dr. Choe:

Please refer to your Biologics License Application (BLA) dated and received on October 5, 2015, submitted under section 351(k) of the Public Health Service Act for CT-P13.

We also refer to your correspondence, dated and received October 5, 2015, requesting review of your proposed proprietary name, Inflectra.

We have completed our review of the proposed proprietary name, Inflectra and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your October 5, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or BsUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- Biosimilar Biological Product Authorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM281991.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Phuong (Nina) Ton, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES  
11/24/2015



BLA 125544

**ACKNOWLEDGE -  
COMPLETE RESPONSE**

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

Attention: Sally Choe, PhD  
Senior Director, Parexel International

Dear Dr. Choe:

We have received your October 5, 2015, resubmission to your biologics license application submitted under section 351(k) of the Public Health Service Act for CT-P13, a proposed biosimilar to US-licensed Remicade (infliximab), on October 5, 2015.

The resubmission contains additional product quality information, including justification report on immunogenicity data from Study CT-P13 1.4, and safety updates that you submitted in response to our June 8, 2015, complete response letter.

We consider this resubmission a complete response to our June 8, 2015, action letter. Therefore, the user fee goal date is April 5, 2016.

If you have any questions, call me at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Nina Ton, PharmD  
Senior Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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PHUONG N TON  
10/14/2015



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** September 25, 2015

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 Advice

Total no. of pages including  
cover and signature page 3

**Comments:** Please acknowledge receipt

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Document to be emailed to: Sally.Choe@parexel.com

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BLA 125544  
CT-P13  
Celltrion, Inc.

Dear Dr. Choe:

Reference is made to your email inquiry dated September 1, 2015, regarding US BLA INN and the new guidance for Nonproprietary Naming of Biological Products. We have the following comments:

We recommend that you submit 3 proposed suffixes, listed in your order of preference, composed of four lowercase letters for use as the distinguishing identifier included in the proper name designated by FDA at such time as your proposed biosimilar to Remicade may be licensed. Your proposed suffixes should be devoid of meaning and follow the recommendations for proposed suffixes in section V of FDA's draft guidance on *Nonproprietary Naming of Biological Products* (see <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf>).

In addition, given that FDA has requested comment in the Notice of Availability for the draft guidance (80 FR 52296, August 28, 2015) on, among other things, the potential benefits and challenges of designating a suffix in the proper name of a biological product that devoid of meaning versus meaningful (e.g., a suffix derived from the name of the license holder), you also may consider proposing 3 additional suffixes that are meaningful (e.g., derived from the name of the prospective license holder) and composed of four lowercase letters. These additional suffixes also should be listed in your order of preference in your submission.

We encourage you to include the proposed suffixes with its response to the June 8, 2015, Complete Response letter, along with any supporting analyses of the proposed suffixes for FDA's consideration based on the factors described in the draft guidance. We will notify you of the suitability of the proposed suffix upon completion of the Agency's evaluation.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/September 25, 2015  
Cleared by: TBBS/September 25, 2015  
LJafari/September 25, 2015  
Finalized by: NTon/September 25, 2015

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/s/  
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PHUONG N TON  
09/25/2015



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** September 10, 2015

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648
<b>Subject:</b> BLA 125544 CT-P13 BPD Type 1 Meeting Minutes Addendum	
Total no. of pages including cover and signature page 3	
<b>Comments:</b> Please acknowledge receipt	

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Document to be emailed to: [Sally.Choe@parexel.com](mailto:Sally.Choe@parexel.com)

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Dear Dr. Choe:

Reference is made the BPD Type 1 meeting held on August 5, 2015, and the official meeting minutes issued on August 26, 2015. Further reference is made to your email inquiry dated September 1, 2015 in which you requested to clarify the meeting discussion for Question 2a.

Based on the information you provided, we have the following clarifying revisions to the discussion for Question 2a as captured in the meeting minutes which are noted in strikethrough and *Italics*:

**Celltrion explained the rationale for using <sup>(b) (4)</sup> μm filters in the previous study and commented that based on their SVP results submitted in the addendum, they do not plan to conduct the dilution studies described in their meeting package. FDA stated that there was a deviation noted during inspection where visible particles were formed when the product was diluted in infusion bag. FDA advised that this risk be mitigated by in-line filtration prior to infusion or other means. FDA also asked for more details of the studies described in the response to the February 27, 2015 IR and how removal of SVPs can be assured using 1.2 μm filtration when the data are derived from studies involving <sup>(b) (4)</sup> μm filters. Celltrion informed FDA that the *SVP visible particulate removal ~~data~~ studies used 1.2 μm filters in response to the deviation noted during the inspection. *SVP Visible particulates were removed equivalently from CT-P13 and reference product by this type of filter. To justify no additional SVP study of dilution for infusion study with 1.2 μm filtration, Celltrion stated that they have MFI subvisible particle data without filtration that showed highly similar results between CT-P13 and US-licensed Remicade (3 lots of each product). Based on this, Celltrion stated that CT-P13 and US-licensed Remicade are highly similar in terms of subvisible particles before filtration, and there was no risk regarding visible particles because Celltrion showed removal of visible particles after filtration during the deviation resolution. FDA asked the Sponsor to include a full description of these study data in the BLA resubmission and also provide a justification in the BLA resubmission for their assertion that no further study is ~~planned~~ necessary.****

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/September 10, 2015  
Cleared by: KBrorson/September 2, 2015  
DFrucht/September 9, 2015  
LJafari/September 10, 2015  
NNikolov/September 10, 2015  
SYim/September 10, 2015  
TBBS/September 10, 2015  
Finalized by: NTon/September 10, 2015

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PHUONG N TON  
09/10/2015



BLA 125544

**MEETING MINUTES**

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

Attention: Sally Choe, PhD  
Senior Director, Parexel International

Dear Dr. Choe:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for CT-P13.

We also refer to the meeting between representatives of your firm and the FDA on August 5, 2015. The purpose of the meeting was to discuss the deficiencies identified in the Complete Response (CR) Letter and your proposed response.

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

If you have any questions, call me at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Nina Ton, PharmD  
Senior Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



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

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Biosimilar  
**Meeting Category:** BPD Type 1

**Meeting Date and Time:** August 5, 2015; 1:00 – 2:00 PM EST  
**Meeting Location:** White Oak Building 22, Conference Room 1311

**Application Number:** BLA 125544  
**Product Name:** CT-P13, a proposed biosimilar to US-licensed Remicade  
**Indication:** CT-P13 is being developed for the same indications as approved for US-licensed Remicade

**Applicant Name:** Celltrion, Inc.

**Meeting Chair:** Badrul A. Chowdhury, MD, PhD  
**Meeting Recorder:** Nina Ton, PharmD

**FDA ATTENDEES**

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)  
Sarah Yim, MD, Supervisory Associate Director, DPARP  
Nikolay Nikolov, MD, Clinical Team Leader, DPARP  
Juwaria Waheed, MD, Clinical Reviewer, DPARP  
Timothy Robison, PhD, Pharmacology/Toxicology Supervisor, DPARP  
Matthew Whittaker, PhD, Pharmacology/Toxicology Reviewer, DPARP  
Ping Ji, PhD, Acting Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)  
Lei He, PhD, Clinical Pharmacology Reviewer, DCPII, OCP  
Ruthanna Davi, PhD, Deputy Director, Division of Biometrics II, Office of Biostatistics (OB)  
Meyiu Shen, PhD, Team Leader, Division of Biometrics VI, Office of Biostatistics (OB)  
Steven Kozolwski, MD, Director, Office of Biotechnology Products (OBP), Office of Pharmaceutical Quality (OPQ)  
David Frucht, MD, Acting Director, Division of Biotechnology Review and Research II (DBRRII), OBP, OPQ  
Kurt Brorson, PhD, Laboratory Chief, DBRRII, OBP, OPQ  
Peter Adams, PhD, Senior Staff Fellow, DBRRII, OBP, OPQ  
Harold Dickensheets, PhD, Team Leader, DBRRII, OBP, OPQ  
William Hallett, PhD, Reviewer, DBRRII, OBP, OPQ  
Cyrus Agarabi, PharmD, PhD, Quality Reviewer, DBRRII, OBP, OPQ

Leah Christl, PhD, Associate Director for Therapeutic Biologics, Therapeutic Biologics and Biosimilars Staff (TBBS)  
Neel Patel, PharmD, Regulatory Project Manager, TBBS  
Tyree Newman, Senior Regulatory Health Project Manager, TBBS  
Janice Weiner, JD, MPH, Senior Regulatory Counsel, Division of Regulatory Policy I (DRP I), Office of Regulatory Policy (ORP)  
Jessica Lee, MD, Medical Officer, Division of Gastroenterology and Inborn Errors Products  
Juli Tomaino, MD, Medical Officer, Division of Gastroenterology and Inborn Errors Products  
Nina Ton, PharmD, Senior Regulatory Project Manager, DPARP

## **SPONSOR ATTENDEES**

### **Celltrion, Inc.**

Elizabeth Pollitt, PhD, Vice President, CMC Regulatory Affairs  
Alexey Kudrin, PhD, MD, Vice President, Clinical Development  
CheHwee Park, MSc, Senior Manager, Regulatory Affairs  
MinKyoung Jeon, PhD, Manager, CMC Regulatory Affairs  
SooYoung Lee, PhD, Director, R&D  
SungHwan Kim, PhD, Manager, R&D  
KyoungHoon Lee, PhD, Senior Manager, R&D  
Dae Seok Choi, PhD, Assistant Manager, CMC Regulatory Affairs  
Eunju Jun, Assistant Manager, CMC Regulatory Affairs

### **Hospira**

Stan Bukofzer, Corporate Vice President and Chief Medical Officer  
Eva Essig, Vice President, Global Regulatory Affairs Biologics

### **Parexel**

Partha Roy, PhD, Director, Regulatory  
Ravi Harapanhalli, PhD, Vice President, CMC (via tcon)  
 (b) (4)  
Arash Adami, PhD, Sr. Associate, Regulatory

## **1. BACKGROUND**

Celltrion submitted a meeting request on June 19, 2015, to the Division of Pulmonary, Allergy, and Rheumatology Products, and the Division granted the meeting on July 1, 2015. The purpose of the meeting was to discuss the deficiencies identified in the Complete Response (CR) Letter and the Sponsor's proposed response. On July 28, 2015, Celltrion sent via email an addendum to the briefing package to provide additional data on subvisible particles, ADCC results from additional lots, and ADCC justification. This addendum was officially submitted to the BLA on August 3, 2015. The Division provided preliminary comments to Celltrion's questions in the briefing package via electronic correspondence dated August 4, 2015. The Division did not review the addendum provided by Celltrion. Arash Adami, Senior Associate Consultant,

Parexel, communicated to the Division via email dated August 4, 2015, that Celltrion requested to focus the meeting discussion on Questions 1a, 1b, 2a, 3a, 3b, 3ci, 3cii, and 5a. Celltrion also provided written responses to the FDA's preliminary comments which are incorporated under the corresponding FDA response. The Sponsor's questions and responses are in *italics*, FDA's responses are in normal font, and the meeting discussion is in **bold**.

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 and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the PHS Act.

## 2. DISCUSSION

### PRODUCT QUALITY

#### Question 1

*To determine whether the observed differences in the subvisible particle (SVP) content (1-5 micron range) in the US-licensed Remicade®, EU-approved Remicade®, and CT-P13 were due to testing a limited number of lots, CELLTRION intends to test an additional ten lots of each product by Micro Flow Imaging (MFI) and light obscuration (HIAC) and provide the results and Tier 2 statistical analysis in the BLA resubmission.*

- a. *Does FDA consider that the number of lots chosen for the test is generally adequate?*
- b. *Does FDA agree that the chosen tests (MFI and HIAC) to determine SVP content are adequate and that no additional orthogonal tests are necessary?*

#### FDA Response

The proposed number of lots for additional testing by MFI and HIAC is generally adequate, but the adequacy of the data will be a review issue.

The chosen tests that will be used to measure SVP are also generally adequate. Currently, there is insufficient information to ascertain the need for additional orthogonal tests. Based on the results of your SVP analysis, additional testing may be needed.

#### Celltrion Response

*We would like to share preliminary data (slides 3-9) from MFI and HIAC testing. These data have been analyzed using Tier 1 equivalence test and show high similarity between CT-P13 and US-licensed Remicade and EU-approved Remicade, at all size ranges under 10 µm (submitted as an addendum to the BPD Type 1 BD on 28 July 2015).*

#### Meeting Discussion

**Celltrion presented an overview of the preliminary data submitted in the July 28, 2015 addendum in slides 3-9. FDA noted that the Agency had received these data the week before and had not had time to review the data in detail. Thus, FDA could not provide**

specific feedback but noted that the new data looked to be trending in the right direction. Celltrion was advised to submit these data to the BLA as a part of the resubmission. The Sponsor asked if additional orthogonal tests are needed, and FDA responded the Agency could not provide a definitive response at this time and the need for additional assays would be a review issue. The Agency noted that there would be interest in further characterization by orthogonal methods in the case that differences in particulate levels between the two product types persisted following analysis of the additional lots, but that this did not appear to be the case based on a preliminary examination of the data submitted in the addendum. Celltrion commented that they planned to analyze the data just submitted using Tier 1 equivalence testing and inquired if this approach would be acceptable. FDA responded that the proposal on the surface seems reasonable, but that statistical analysis would be a review issue once the data are submitted.

### **Question 2**

*The results of testing of additional lots of each product for SVP content may either reconfirm the earlier results, or may lead to diminished differences; but may not result in statistical high similarity. In such an event, CELLTRION will conduct SVP analysis of product samples representative of product diluted as for infusion. Given that for both CT-P13 and the reference products an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2  $\mu\text{m}$  or less) is included in the infusion set according to the US Prescribing Information (USPI) of the reference product, CELLTRION will also perform studies to determine the effect of dilution for infusion and infusion set filters on SVP content of each product. Data and statistical analysis of the results will be provided to determine the SVP levels of the products in these settings. Thus, CELLTRION will determine whether the 1.2  $\mu\text{m}$  filters (i) result in similar levels of SVP in the 3 products and (ii) reduce the levels to acceptably low levels.*

- a. *Does FDA agree with this approach?*

### **FDA Response**

The approach is generally acceptable.

If differences in the levels of subvisible particulates in the size range of 1-5 microns are confirmed between the products after testing the additional lots, further characterization of the nature and composition of the subvisible particulates should be performed. Based on this information, a risk-based analysis focused on patient safety should be provided as part of your response to address the issue of SVPs outlined in the CR letter.

In addition, the studies described in your response to the information request (IR) dated February 27, 2015, described the in-line infusion set as a (b)(4)  $\mu\text{m}$  filter, while the proposed studies in this submission describe the in-line infusion set as containing a 1.2  $\mu\text{m}$  filter. Clarify this discrepancy, and provide more information on the in-line infusion set filters in the previous studies, in the proposed studies, and how the data generated from the studies described in the February 27, 2015 IR will relate to the studies proposed in this submission. Additionally, provide information describing any integrity testing that will occur on these filters following product administration.

### **Celltrion Response**

*As high similarity between the products in SVP content has been shown using Tier 1 analysis, CLT does not intend to conduct the small dilution from diffusion and filtration study.*

*For information, (b) (4)  $\mu\text{m}$  filters were used in analysis of lots used in Study CT-P13 1.4 because this filter size was used throughout this clinical study. However, CLT recognize that the USPI (2015) for US-licensed Remicade allows use of in-line filters of 1.2  $\mu\text{m}$  and below.*

### **Meeting Discussion**

**Celltrion explained the rationale for using (b) (4)  $\mu\text{m}$  filters in the previous study and commented that based on their SVP results submitted in the addendum, they do not plan to conduct the dilution studies described in their meeting package. FDA stated that there was a deviation noted during inspection where visible particles were formed when the product was diluted in infusion bag. FDA advised that this risk be mitigated by in-line filtration prior to infusion or other means. FDA also asked for more details of the studies described in the response to the February 27, 2015 IR and how removal of SVPs can be assured using 1.2  $\mu\text{m}$  filtration when the data are derived from studies involving (b) (4)  $\mu\text{m}$  filters. Celltrion informed FDA that the SVP removal data used 1.2  $\mu\text{m}$  filters in response to the deviation noted during the inspection. SVP were removed equivalently from CT-P13 and reference product by this type of filter. FDA asked the Sponsor to include a full description of these study data in the BLA resubmission and also provide a justification if no further study is planned.**

*b. Does FDA recommend any particular statistical analysis for this data set?*

### **FDA Response**

No, we do not recommend any particular statistical analysis for this data set (see the response to Question 2a). You should justify your approach.

### **Meeting Discussion**

**This question was not discussed.**

*c. If minor differences in the SVP content are confirmed by the above studies, what additional testing does FDA recommend to further substantiate the 3-way quality similarity studies conducted to date?*

### **FDA Response**

Refer to the response to Question 2a. Provide justification that the differences in SVPs in the range of 1 to 5 microns have minimal patient safety impact. The adequacy of the data will be a review issue.

### **Meeting Discussion**

**This question was not discussed.**

**Question 3**

*To determine whether the observed differences in the Antibody-Dependent Cellular Cytotoxicity (ADCC) results in the natural killer (NK) cell assay were due to testing of a limited number of lots, CELLTRION intends to test additional lots of each product and provide the results in the BLA resubmission.*

- a. *Does FDA consider that the number of lots chosen for the test is generally adequate?*

**FDA Response**

You propose to test 20 additional lots of US-licensed Remicade and EU-approved infliximab along with 13 additional lots of CT-P13. These data will be combined with the ADCC data that have already been submitted for a total of 26 lots of CT-P13, 33 lots US-licensed Remicade and 30 lots of EU-approved infliximab. The number of lots proposed for each product appears to be adequate, but the adequacy of the data will be a review issue.

**Celltrion Response**

*We would like to present the data (slides 11-15) available from analysis of ADCC NK cell of additional lots. These data have been analyzed using Tier 2 approach and demonstrate high similarity between CT-P13 and US-licensed Remicade and between EU-approved and US-licensed Remicade in NK cell ADCC activity.*

**Meeting Discussion**

**See meeting discussion below Question 3b.**

- b. *Does FDA agree that if additional testing shows high similarity results using Tier 2 statistical analysis, [REDACTED] (b) (4) [REDACTED] ?*

**FDA Response**

We agree that Tier 2 quality range testing is appropriate for the evaluation of ADCC assay data. [REDACTED] (b) (4)

[REDACTED] While testing additional lots of CT-P13 and US-licensed Remicade for ADCC activity and results that support a demonstration that the products are highly similar in terms of ADCC based on an appropriate Tier 2 statistical analysis would address the articulated deficiency in part, we also request that you identify the critical product quality attributes that correlate with the NK cell-dependent ADCC activity of CT-P13 and demonstrate that your process has control over these attributes. To address the question of analytical similarity with respect to NK cell-dependent ADCC activity, you should also include the following data in your response: (1) figures demonstrating ADCC killing curves for each lot (cytotoxicity vs. drug concentration); and (2) aggregate results of CT-P13 ADCC activity compared to US-licensed Remicade or EU-approved infliximab, respectively, along with a Tier 2 statistical analysis. In addition, because FcγRIIIa binding is proximal to NK cell-dependent ADCC and is readily quantifiable, and because differences were noted in FcγRIIIa binding between CT-P13, US-licensed Remicade and EU-approved infliximab in your original 351(k) BLA (refer to FDA's response to Question 3c(ii)), you should also include a comparative assessment of FcγRIIIa as part of your response.

### **Celltrion Response**

*We will present data (slides 11-15) showing Tier 2 analysis of additional lots.*

*CLT have data analysis from additional lots (submitted as an addendum to the BPD Type 1 BD on 28 July 2015), which show using Tier 2 quality range statistical analysis high similarity between CT-P13 and US-licensed Remicade, for ADCC NK cell activity. CLT does recognize that a small difference in mean values of absolute cytotoxicity of 3-4% and of relative activity of 12-19% remains. CLT considers that similarity of CT-P13 and US-licensed Remicade in ADCC NK cell activity has been adequately addressed. Does FDA agree?*

*We intend to submit the data for (1) figures demonstrating ADCC killing curves for each lot (cytotoxicity vs. drug concentration); and (2) aggregate results of CT-P13 ADCC activity compared to US-licensed Remicade or EU-approved infliximab, respectively, along with a Tier 2 statistical analysis. In additional, we will present FcγRIIIa binding affinity data for additional lots in the BLA resubmission.*

### **Meeting Discussion**

**Celltrion presented the data submitted in the July 28, 2015 addendum in slides 11-15 and asked if the ADCC issue had been adequately addressed. FDA responded that the Agency had only received the data the week before and had not reviewed the data in detail. FDA noted that while the acceptability of the data will be a review issue, the data appear to be trending in the right direction. FDA recommended that the Sponsor should present the correlative data in a format such as a scatter plot to compare the data and judge the tightness of the correlation. Celltrion described that the original ADCC killing curve was based on an in-house reference standard, and that the original curve was used to select concentrations to test further. Therefore, Celltrion will not have full curves for the additional lots tested. FDA noted that Celltrion should provide a description of the ADCC killing curves, including information on the error bars and testing of duplicates.**

**FDA advised Celltrion that even if the additional data support a demonstration that the products are highly similar in terms of ADCC, Celltrion should develop a control strategy for lot release to exclude lots that would be outliers and tighten specifications for FcγRIIIa binding to ensure that CT-P13 will remain highly similar for ADCC activity. FDA noted that FcγRIIIa testing employed as a release test can be used to exclude release of lots that would fall outside of the +/- 3SD range for ADCC activity if these two attributes are tightly correlated.**

- c. If statistical differences in ADCC are re-confirmed, CELLTRION will attempt to identify the quality attributes that underlie ADCC activity of CT-P13. Specifically, CELLTRION will assess the potential link between afucosylation, non-glycosylation, H2L1 variant content and level of high molecular weight (HMW) forms with ADCC activity. NK ADCC assays will be performed using CT-P13 with different levels of each of these 4 quality attributes. The oligosaccharide profile, level of non-glycosylated product, level of intact IgG and H2L1 variant, as well as level of HMW forms of all samples will be determined.*
  - i. Does FDA agree with this approach?*

### **FDA Response**

Your proposal to identify the structural basis for the differences between CT-P13 and US-licensed Remicade that could underlie apparent differences in FcγRIIIa binding and downstream ADCC activity is, in general, reasonable. We also recommend including an assessment of the degree of glycation of CT-P13 and US-licensed Remicade, since differences in glycation may impact ADCC as well. However, we expect that you would include these data in your response irrespective of whether differences in ADCC activity are re-confirmed with the inclusion of additional lots.

### **Meeting Discussion**

**Celltrion noted that they will analyze the 4 quality attributes described in Question 3c and how they correlate with ADCC. FDA acknowledged Celltrion's plan and noted that understanding the structural correlates for ADCC will help in the creation of an appropriate control strategy to ensure consistent manufacturing of a highly similar product.**

**Celltrion stated their intent to test all additional batches for overall glycation level and an in-depth analysis including site characterization on 3 lots of each product. FDA agreed with this strategy given the level of complexity involved. FDA noted that if Celltrion wanted to claim that glycation occurs rapidly *in vivo* and thus not an important quality attribute to control, having *in vivo* data to support this contention will be helpful for interpretation.**

- ii. *Are there any additional quality attributes that FDA recommend CELLTRION test for presumed linkage to ADCC activity?*

### **FDA Response**

Refer to FDA's responses to Questions 3b and 3c(i).

Based on the data provided in the original 351(k) BLA, differences were noted in the FcγRIIIa binding capability of CT-P13, US-licensed Remicade and EU-approved infliximab. Since it is likely that differences in FcγRIIIa binding are linked to the apparent difference in ADCC, assess the contribution of the four quality attributes listed in the body of Question 3 to FcγRIIIa binding.

### **Celltrion Response**

*We acknowledge your response and we intend to submit the data for the four quality attributes listed in the body of Question 3 and the FcγRIIIa data for the additional lots that have been included in ADCC analysis in the BLA resubmission. CLT has also prepared samples containing different levels of each of these four quality attributes, which have been tested in the ADCC assay. CLT intends to test these samples containing varied levels of the four quality attributes in the FcγRIIIa binding affinity assay, however, due to low sample availability and technical difficulties, in analyzing FcγRIIIa of aggregated and H2L1 samples, CLT cannot commit to providing data showing correlation between aggregates or H2L1 with FcγRIIIa binding affinity.*

### **Meeting Discussion**

Celltrion discussed that while they plan to test the four quality attributes described, they will not have sufficient enriched samples for all possible assay combinations. In the case of correlating ADCC to aggregation state, Celltrion stated that the assessment is limited by solubility issues. They asked if eliminating this combination from the analysis is acceptable. FDA asked if there was a solubility issue with H2L1 and the Sponsor answered no. FDA stated that it would be preferable to assess the H2L1 variant with respect to FcγRIIIa binding over ADCC if the supply of the H2L1 variant were limited, as FcγRIIIa binding is proximal to ADCC activity and would provide a more precise assessment of similarity. FDA noted that nevertheless, it would be preferable to have both ADCC and FcγRIIIa binding data for the H2L1 variant. FDA requested that the Sponsor provide ADCC and FcγRIIIa binding data for each of the lots evaluated in the analytical similarity assessment, preferably in a side-by-side tabular format. The Sponsor further asked if the inability to provide H2L1 correlative data would be an approvability issue. FDA responded that the acceptability of the analysis would be a review issue. FDA advised Celltrion to provide justification if correlative data for all 4 quality attributes and ADCC could not be generated. FDA advised Celltrion that the Agency considered it necessary to demonstrate that ADCC is highly similar between CT-P13 and the US-licensed reference product. In addition, Celltrion was advised to determine the structural basis for ADCC activity in their product and develop a control strategy to ensure that ADCC remains highly similar during future manufacturing.

### **Question 4**

*Depending on the data obtained, CELLTRION will*

(b) (4)

[REDACTED]

*Does FDA agree with this strategy?*

### **FDA Response**

We do not agree with this strategy. To ensure that CT-P13 is highly similar to US-licensed Remicade, you should provide a scientific rationale that your proposed control strategy will be appropriate to meet this expectation. In the absence of identifying a structural basis underlying the observed differences in ADCC, we do not think it likely that this expectation could be met.

### **Meeting Discussion**

**This question was not discussed.**

### **Question 5**

*If the additional ADCC testing does not lead to statistical high similarity in ADCC activity using NK effector cell between CT-P13, EU-approved and US-licensed Remicade®, CELLTRION will*

*provide updated literature (where available) and all in-house data and justification further substantiating our position that observed differences in ADCC do not play a clinically meaningful role in the potency of infliximab's mechanism of action (MoA) for the proposed clinical indications. However, in order to provide 'an adequate justification, including an evaluation of the role of ADCC particularly in the setting of inflammatory bowel disease', CELLTRION would like to ask FDA:*

- a. In which specific aspects were the justifications submitted in the initial BLA not acceptable, or considered inadequate?*

### **FDA Response**

As stated previously, the results of your statistical testing should support that CT-P13 and US-licensed Remicade NK cell-dependent ADCC and Fc $\gamma$ RIIIa binding are highly similar. The justifications provided in the original BLA did not provide adequate evidence to support that NK cell-dependent ADCC and Fc $\gamma$ RIIIa binding are highly similar between CT-P13 and US-licensed Remicade.

We have recommended that NK cell-dependent ADCC be evaluated using Tier 2 quality range testing. We are also recommending that Fc $\gamma$ RIIIa binding be evaluated using an appropriate statistical approach. Data from your testing of the reference product should be used to determine the acceptance criteria to support a demonstration that the products are highly similar.

### **Celltrion Response**

*CLT has data from additional lots (slides 11-15; submitted as an addendum to the BPD Type 1 BD on 28 July 2015), which show, using Tier 2 quality range statistical analysis, high similarity between CT-P13 and US-licensed Remicade, in ADCC NK cell activity. Analysis of Fc $\gamma$ RIIIa binding affinity of additional lots using SPR may or may not show high similarity between CT-P13 and US-licensed Remicade. Data available to date for Fc $\gamma$ RIIIa binding affinity show that the physiological relevance of absolute difference in mean values of CT-P13 and US-licensed Remicade is rather limited in the context of differences observed between Remicade binding to Fc $\gamma$ RIIIa receptors of different isotypes and the orders of magnitude difference in binding to Fc $\gamma$  receptors of all types. However, given high similarity has been demonstrated for ADCC NK cell activity, any small difference observed in Fc $\gamma$ RIIIa binding affinity has no functional impact. Thus, the ADCC data provide assurance of no clinically meaningful impact.*

*CLT considers that an additional evaluation and justification of the role of ADCC across all conditions of use, particularly in the setting of IBD in relation to clinical activity, is no longer necessary. Does FDA agree?*

### **Meeting Discussion**

**Celltrion discussed that they believe that they have addressed the question of ADCC similarity in the data provided in the July 28, 2015 meeting package addendum, and the role of ADCC in the MoA of infliximab in the position paper included in the original BLA submission. Celltrion asked if there are additional aspects that FDA thinks need to be addressed and noted that they believe that the additional analysis provided in the July 28, 2015 addendum addresses the issues concerning the position paper outlined in FDA's**

**response. FDA responded that they did not agree with Celltrion's position that there was no need to further address the role of ADCC (refer to further discussion below).**

**The Agency noted that a determination of a direct correlation between ADCC and FcγRIIIa binding and/or other quality attributes could be used to inform Celltrion's control strategy. Celltrion stated that their data to date showed a good correlation between ADCC and FcγRIIIa binding; the data were summarized on slide 17. FDA commented that the Agency would want to see the distribution of lot data for FcγRIIIa. FDA repeated the recommendation that Celltrion develop an appropriate control strategy to exclude lots that would be outliers.**

**FDA Response (continued)**

However, if the results of your statistical testing of these attributes despite the addition of more lots are outside the pre-specified acceptance criteria, you may consider at that time providing updated literature and all in-house data to justify that the observed differences do not preclude a demonstration of highly similar. The adequacy of this justification, along with the proposal and demonstration of an appropriate control strategy, will be a review issue.

With respect to your proposal to address the differences in the ADCC assay in the context of extrapolation to all indications, we have the following comments: We have reviewed your "Position Paper on the Extrapolation of CT-P13 Data to Indications for which Licensure is Sought". We understand that you believe that TNF sequestration is the primary function for infliximab, and that reverse signaling is the primary Fc-based function in IBD. We also understand that you contend that ADCC plays a minimal role in infliximab efficacy in IBD.

We believe that some key observations in the medical literature were not addressed. These observations could lead to alternative conclusions regarding the role of Fc effector functions (including ADCC) in the mechanism of action of anti-TNF therapies in the setting of IBD.

Specifically, you contend that the activity of TNF blockers with reduced or absent Fc function still possess efficacy in IBD. You cite certolizumab pegol (Cimzia, a pegylated humanized Fab' fragment that lacks an Fc component) as effective for IBD treatment, implying that Fc effector functions (including ADCC) are not required for the clinical activity of TNF blockers, including infliximab, in this group of patients. However, you did not address other relevant data in the scientific literature:

- I. Although approved for use as a maintenance therapy for Crohn's disease, clinical trials to demonstrate efficacy of certolizumab pegol in inducing remission in Crohn's disease did not reach statistical significance (Sandborn et al, NEJM, 2007 and Sandborn et al, Clinical Gastroenterology and Hepatology, 2011). However, Cimzia did demonstrate statistically significant remission in Crohn's disease at Week 26 vs. placebo in two separate studies, as described in the Cimzia USPI. In the absence of randomized data between certolizumab and infliximab, and taking into account the differences seen in the activity of certolizumab in IBD, there may be some differences in clinical response between certolizumab pegol and the anti-TNF mAbs, and thus ADCC cannot be ruled out

as a contributory factor to efficacy in IBD. A discussion of these points should have been included in the position paper.

- II. Several TNF-alpha blockers lacking or having attenuated Fc function have failed clinical trials for the Crohn's disease indication, arguing for the importance of intact Fc function for efficacy in IBD. These cases were omitted from the position paper. Several examples are included below.
  - a. Etanercept, an Fc-TNFRp75 fusion protein (lacking the CH1 domain), failed to show any clinical response in active Crohn's disease (Sandborn et al, Gastroenterology, 2001). It should be noted that Etanercept has been shown to be capable of inducing ADCC *in vitro*, albeit, at a reduced level compared to Remicade (Mitoma et al, Arthritis & Rheumatism, 2008) (Arora et al, Cytokine 2009)
  - b. CDP571, an intact IgG4 targeting TNFa, failed to induce a statistically significant long term clinical response in moderate to severe Crohn's disease (Sandborn et al, Gut, 2004). Human IgG4 antibodies, while structurally similar to IgG1 antibodies like infliximab, differ in that they possess low ADCC inducing activity (Murphy, Janeway's Immunobiology 8<sup>th</sup> ed, 2012).
  - c. Onercept, a soluble TNFRp55 receptor protein, failed to induce remission in patients with active Crohn's disease (Rutgeerts et al, Clinical Gastroenterology and Hepatology, 2006).

### **Celltrion Response**

*CLT acknowledges FDA's comments on the extrapolation paper submitted in the initial BLA. CLT recognizes differences in structural and functional aspects of TNF inhibitors, which were approved in IBD indications or failed in clinical studies and terminated during development phases.*

*Given the high similarity in ADCC activity detected using additional lots, CLT is not planning to update the extrapolation paper (or provide an additional appendix) to reflect these comments. Does the FDA agree?*

### **Meeting Discussion**

**Celltrion repeated their intent not to update the position paper submitted in the original BLA; however, FDA commented that the Agency is interested in the broad analysis of MoA and again advised the Sponsor to address the points outlined in FDA's response addressing Celltrion's position and alternate views. FDA noted that such a comprehensive analysis and justification would support the appropriateness of a control strategy for ADCC. FDA also noted that the issue of extrapolation will likely be discussed at the AC meeting, and Celltrion should be prepared with a comprehensive assessment.**

- b. What additional discussion of factors or elements already included in dossier Section 5.3.5.4 and additional Information Request (IR) responses does FDA expect to be*

*included in the 'adequate justification, including an evaluation of the role of ADCC particularly in the setting of inflammatory bowel disease, that the observed difference in ADCC is not relevant to clinical activity'?*

**FDA Response**

Refer to FDA's response to Question 5a. You should address the comments provided in the response to Question 5a, comments (I) and (II) as an appendix to a revised "Position Paper on the Extrapolation of CT-P13 Data to Indications for which Licensure is Sought".

**Meeting Discussion**

**This question was not discussed.**

- c. *What additional factors or elements NOT previously included in dossier Section 5.3.5.4 and in IR responses does FDA expect to be considered and included in the 'adequate justification, including an evaluation of the role of ADCC particularly in the setting of inflammatory bowel disease, that the observed difference in ADCC is not relevant to clinical activity'?*

**FDA Response**

See responses to Questions 5a and 5b.

**Meeting Discussion**

**This question was not discussed.**

**SAFETY UPDATE**

**Question 6**

*CELLTRION would like to clarify the extent and the format of the safety update to be included in the BLA resubmission. Does FDA agree with the proposed plan for the safety update outlined in this briefing document?*

**FDA Response**

Your proposal is reasonable. We also recommend including tables specific for adverse events of special interest.

**Meeting Discussion**

**This question was not discussed.**

**IMMUNOGENICITY**

**Question 7**

*For comment #1 relating to the immunogenicity seen in the healthy volunteer PK study, CELLTRION has conducted a root cause analysis to determine if there are any systematic reasons for the observations in the study. None were identified. The rationale supporting*

*similarity of immunogenicity profiles of CT-P13 and US-licensed Remicade® rely on the totality of evidence in the program. We acknowledge that CT-P13 1.4 was the only study that used US-licensed Remicade®, and will further justify the rationale given in the initial BLA (Module 5, Section 5.3.5.4, Report on Immunogenicity Results from CT-P13 1.4 Study) and subsequent IR responses (SN0027 and SN0031). However, in order to provide ‘a rationale for why the results from study CT-P13 1.4 are in alignment with the conclusion that the immunogenicity profiles of CT-P13 and US-licensed Remicade® are similar’ CELLTRION would like to ask FDA if there are any additional factors or elements FDA consider important and pertinent to include in this rationale.*

### **FDA Response**

If biophysical differences (i.e. subvisible particulates) are ruled out as a cause for the observed differences between CT-P13 and US-licensed Remicade, the immunogenicity data generated using EU-approved infliximab could be used to address the residual uncertainty regarding immunogenicity. This would support a demonstration of no clinically meaningful differences between US-licensed Remicade and CT-P13 in terms of immunogenicity, assuming an adequate scientific bridge is provided.

### **Meeting Discussion**

**This question was not discussed.**

## **STABILITY DATA**

### **Question 8**

*For comment #2 in regards to the stability data to support CT-P13 expiry date, CELLTRION wishes to clarify that the 36-57 months of stability data were submitted for the Process B DS batches manufactured by different DP manufacturing sites as part of the BLA amendment on 31 March 2015 (Section 3.2.P.8.3, from Table 3.2.P.8.3-1 to Table 3.2.P.8.3-12). Could FDA clarify whether:*

- a. FDA expects DP shelf-life to be based on stability data from DP lots manufactured using Process B DS material?*
- b. DP stability data (DP lots manufactured with Process B DS) from all DP manufacturing sites can be used to support the proposed shelf-life of CT-P13 DP?*
- c. If not, could FDA clarify which DP site lots (manufactured using Process B DS) may be used to support CT-P13 shelf-life claim?*

### **FDA Response**

Our statement that current DP stability data using Process B batches of CT-P13 DS support an expiry date of 42 months, not <sup>(b)</sup><sub>(4)</sub> months, was based on data submitted from drug product produced in Celltrion <sup>(b)</sup><sub>(4)</sub> months as of time of review) <sup>(b)</sup><sub>(4)</sub> by the batches produced at other facilities (i.e., Rentschler, Binex).

Stability data from batches produced at commercial sites are considered to be conclusive for expiry claims. Stability data from pilot sites are considered supportive from the standpoint of

(b) (4)

### **Meeting Discussion**

**This question was not discussed.**

## **REGULATORY**

### **Question 9**

*The resubmission covering responses and supporting data for all the deficiencies noted in the CR letter is planned to be submitted by the end of August, 2015. It is CELLTRION's understanding that the BLA review can proceed focusing on the issues raised in the CR letter and that the original submission will not be re-reviewed nor the previously resolved issues will be brought up for further resolution unless the resubmitted data triggers such a review. Does FDA agree with this understanding? Does FDA also confirm that the resubmission will be subject to a six-month review clock?*

### **FDA Response**

The review of your resubmission will be focused on your responses to the deficiencies and comments articulated in the CR letter and the supporting data you submit. However, this information will be reviewed in the context of the totality of the evidence submitted as a part of your 351(k) BLA. Therefore, as part of this review, we may revisit already reviewed information that is relevant to the issues.

The timing of the review clock is subject to the adequacy of your complete response. However, if the resubmission constitutes a complete response addressing all the deficiencies outlined in the CR letter, we agree that per BsUFA it will be subject to a six-month review clock.

### **Meeting Discussion**

**This question was not discussed.**

### **Question 10**

*CELLTRION assumes FDA will still seek advice from the Arthritis Advisory Committee, which has a tentative meeting date of October 23, 2015. Assuming CELLTRION resubmits the BLA by August 2015, will FDA consider inclusion of CELLTRION's BLA for that meeting? If not, what is the earliest expected date for the Advisory Committee meeting? Assuming all major issues from the CR letter are resolved during the first half of the six-month clock, will the Advisory Committee meeting occur within the second half of the review clock?*

### **FDA Response**

At this time, FDA cannot provide additional information regarding the timing of an Advisory Committee meeting. The scheduling of an Advisory Committee meeting would depend on

multiple factors, including the timing of your submission, the adequacy of the data submitted, and the time needed to prepare for such a meeting.

### **Meeting Discussion**

**This question was not discussed.**

### **Additional Comment**

In your “Position Paper on the Extrapolation of CT-P13 Data to Indications for which Licensure is Sought” (page 151), you state that you plan to perform a clinical study comparing CT-P13 and US-licensed Remicade in Crohn’s Disease patients. Please describe the timeframe of completion of this clinical study and provide a summary of the design.

### **Meeting Discussion**

**Celltrion stated that the study in patients with Crohn’s Disease is ongoing, and data at week 30 and 54 will be available in 2016; however, it may not be available to include in the BLA resubmission but will submit this data to the IND. FDA acknowledged Celltrion’s response and noted that they were not asking for the data as a part of the resubmission to address the CR issues.**

**Celltrion commented that they have data from more than 5000 patients treated with CT-P13 outside the US and asked FDA if they should include this uncontrolled data in the resubmission. FDA encouraged the Sponsor to submit any data they consider relevant to support their application.**

### **Additional Meeting Discussion**

**FDA asked Celltrion about the projected timing of their resubmission. Celltrion responded that due to additional time needed to test more samples based on the comments from FDA, the resubmission would be delayed by 3 to 4 weeks. FDA confirmed that the resubmission will have a six-month review clock per BsUFA and asked Celltrion to provide an update of their resubmission timeline when available for the purpose of planning the AC meeting.**

## **3. ADDITIONAL INFORMATION**

### **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 (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team ([cdcr-edata@fda.hhs.gov](mailto:cdcr-edata@fda.hhs.gov)) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page 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.

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 start 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 Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

#### **4. ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

**5. ACTION ITEMS**

There were no action items.

**6. ATTACHMENTS AND HANDOUTS**

The slides presented at the meeting are attached.

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PHUONG N TON  
08/26/2015



BLA 125544

**MEETING PRELIMINARY COMMENTS**

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

Attention: Sally Choe, PhD  
Senior Director, Parexel International

Dear Dr. Choe:

Please refer to your Biologic License Application (BLA) submitted under section 351(k) of the Public Health Service Act for CT-P13.

We also refer to your June 19, 2015, correspondence, received June 19, 2015, requesting a Biosimilar Biological Product Development (BPD) Type 1 meeting to discuss the deficiencies identified in the Complete Response (CR) Letter and your proposed response.

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) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Nina Ton, PharmD  
Senior Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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## PRELIMINARY MEETING COMMENTS

**Meeting Type:** Biosimilar  
**Meeting Category:** BPD Type 1

**Meeting Date and Time:** August 5, 2015; 1:00 – 2:00 PM EST  
**Meeting Location:** White Oak Building 22, Conference Room 1311

**Application Number:** BLA 125544  
**Product Name:** CT-P13, a proposed biosimilar to US-licensed Remicade  
**Indication:** CT-P13 is being developed for the same indications as approved for US-licensed Remicade  
**Applicant Name:** Celltrion, Inc.

### 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 August 5, 2015, from 1:00 to 2:00 PM at White Oak campus between Celltrion Inc. and the Division of Pulmonary, Allergy, and Rheumatology Products. 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.

## 1. BACKGROUND

Celltrion submitted a BPD Type 1 meeting request on June 19, 2015, to the Division of Pulmonary, Allergy, and Rheumatology Products, and the Division granted the meeting on July

1, 2015. The purpose of the meeting is to discuss the deficiencies identified in the Complete Response Letter and the sponsor's proposed response. The briefing package was also submitted with the meeting request.

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 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. QUESTIONS AND RESPONSES**

### **PRODUCT QUALITY**

#### **Question 1**

*To determine whether the observed differences in the subvisible particle (SVP) content (1-5 micron range) in the US-licensed Remicade®, EU-approved Remicade®, and CT-P13 were due to testing a limited number of lots, CELLTRION intends to test an additional ten lots of each product by Micro Flow Imaging (MFI) and light obscuration (HIAC) and provide the results and Tier 2 statistical analysis in the BLA resubmission.*

- a. Does FDA consider that the number of lots chosen for the test is generally adequate?*
- b. Does FDA agree that the chosen tests (MFI and HIAC) to determine SVP content are adequate and that no additional orthogonal tests are necessary?*

#### **FDA Response**

The proposed number of lots for additional testing by MFI and HIAC is generally adequate, but the adequacy of the data will be a review issue.

The chosen tests that will be used to measure SVP are also generally adequate. Currently, there is insufficient information to ascertain the need for additional orthogonal tests. Based on the results of your SVP analysis, additional testing may be needed.

#### **Question 2**

*The results of testing of additional lots of each product for SVP content may either reconfirm the earlier results, or may lead to diminished differences; but may not result in statistical high similarity. In such an event, CELLTRION will conduct SVP analysis of product samples representative of product diluted as for infusion. Given that for both CT-P13 and the reference products an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less) is included in the infusion set according to the US Prescribing Information (USPI) of the reference product, CELLTRION will also perform studies to determine the effect of dilution for infusion and infusion set filters on SVP content of each product. Data and statistical analysis of the results will be provided to determine the SVP levels of the products in these*

*settings. Thus, CELLTRION will determine whether the 1.2 µm filters (i) result in similar levels of SVP in the 3 products and (ii) reduce the levels to acceptably low levels.*

*a. Does FDA agree with this approach?*

**FDA Response**

The approach is generally acceptable.

If differences in the levels of subvisible particulates in the size range of 1-5 microns are confirmed between the products after testing the additional lots, further characterization of the nature and composition of the subvisible particulates should be performed. Based on this information, a risk-based analysis focused on patient safety should be provided as part of your response to address the issue of SVPs outlined in the CR letter.

In addition, the studies described in your response to the information request (IR) dated February 27, 2015, described the in-line infusion set as a (b) (4) µm filter, while the proposed studies in this submission describe the in-line infusion set as containing a 1.2 µm filter. Clarify this discrepancy, and provide more information on the in-line infusion set filters in the previous studies, in the proposed studies, and how the data generated from the studies described in the February 27, 2015 IR will relate to the studies proposed in this submission. Additionally, provide information describing any integrity testing that will occur on these filters following product administration.

*b. Does FDA recommend any particular statistical analysis for this data set?*

**FDA Response**

No, we do not recommend any particular statistical analysis for this data set (see the response to Question 2a). You should justify your approach.

*c. If minor differences in the SVP content are confirmed by the above studies, what additional testing does FDA recommend to further substantiate the 3-way quality similarity studies conducted to date?*

**FDA Response**

Refer to the response to Question 2a. Provide justification that the differences in SVPs in the range of 1 to 5 microns have minimal patient safety impact. The adequacy of the data will be a review issue.

**Question 3**

*To determine whether the observed differences in the Antibody-Dependent Cellular Cytotoxicity (ADCC) results in the natural killer (NK) cell assay were due to testing of a limited number of lots, CELLTRION intends to test additional lots of each product and provide the results in the BLA resubmission.*

*a. Does FDA consider that the number of lots chosen for the test is generally adequate?*

**FDA Response**

You propose to test 20 additional lots of US-licensed Remicade and EU-approved infliximab along with 13 additional lots of CT-P13. These data will be combined with the ADCC data that have already been submitted for a total of 26 lots of CT-P13, 33 lots US-licensed Remicade and 30 lots of EU-approved infliximab. The number of lots proposed for each product appears to be adequate, but the adequacy of the data will be a review issue.

- b. *Does FDA agree that if additional testing shows high similarity results using Tier 2 statistical analysis, [REDACTED] (b) (4) [REDACTED] ?*

**FDA Response**

We agree that Tier 2 quality range testing is appropriate for the evaluation of ADCC assay data. [REDACTED] (b) (4)

[REDACTED] While testing additional lots of CT-P13 and US-licensed Remicade for ADCC activity and results that support a demonstration that the products are highly similar in terms of ADCC based on an appropriate Tier 2 statistical analysis would address the articulated deficiency in part, we also request that you identify the critical product quality attributes that correlate with the NK cell-dependent ADCC activity of CT-P13 and demonstrate that your process has control over these attributes. To address the question of analytical similarity with respect to NK cell-dependent ADCC activity, you should also include the following data in your response: (1) figures demonstrating ADCC killing curves for each lot (cytotoxicity vs. drug concentration); and (2) aggregate results of CT-P13 ADCC activity compared to US-licensed Remicade or EU-approved infliximab, respectively, along with a Tier 2 statistical analysis. In addition, because FcγRIIIa binding is proximal to NK cell-dependent ADCC and is readily quantifiable, and because differences were noted in FcγRIIIa binding between CT-P13, US-licensed Remicade and EU-approved infliximab in your original 351(k) BLA (refer to FDA's response to Question 3c(ii)), you should also include a comparative assessment of FcγRIIIa as part of your response.

- c. *If statistical differences in ADCC are re-confirmed, CELLTRION will attempt to identify the quality attributes that underlie ADCC activity of CT-P13. Specifically, CELLTRION will assess the potential link between afucosylation, non-glycosylation, H2L1 variant content and level of high molecular weight (HMW) forms with ADCC activity. NK ADCC assays will be performed using CT-P13 with different levels of each of these 4 quality attributes. The oligosaccharide profile, level of non-glycosylated product, level of intact IgG and H2L1 variant, as well as level of HMW forms of all samples will be determined.*
- i. *Does FDA agree with this approach?*

**FDA Response**

Your proposal to identify the structural basis for the differences between CT-P13 and US-licensed Remicade that could underlie apparent differences in FcγRIIIa binding and downstream ADCC activity is, in general, reasonable. We also recommend including an assessment of the degree of glycation of CT-P13 and US-licensed Remicade, since differences in glycation may

impact ADCC as well. However, we expect that you would include these data in your response irrespective of whether differences in ADCC activity are re-confirmed with the inclusion of additional lots.

- ii. *Are there any additional quality attributes that FDA recommend CELLTRION test for presumed linkage to ADCC activity?*

**FDA Response**

Refer to FDA's responses to Questions 3b and 3c(i).

Based on the data provided in the original 351(k) BLA, differences were noted in the FcγRIIIa binding capability of CT-P13, US-licensed Remicade and EU-approved infliximab. Since it is likely that differences in FcγRIIIa binding are linked to the apparent difference in ADCC, assess the contribution of the four quality attributes listed in the body of Question 3 to FcγRIIIa binding.

**Question 4**

*Depending on the data obtained, CELLTRION will* (b) (4)



*Does FDA agree with this strategy?*

**FDA Response**

We do not agree with this strategy. To ensure that CT-P13 is highly similar to US-licensed Remicade, you should provide a scientific rationale that your proposed control strategy will be appropriate to meet this expectation. In the absence of identifying a structural basis underlying the observed differences in ADCC, we do not think it likely that this expectation could be met.

**Question 5**

*If the additional ADCC testing does not lead to statistical high similarity in ADCC activity using NK effector cell between CT-P13, EU-approved and US-licensed Remicade®, CELLTRION will provide updated literature (where available) and all in-house data and justification further substantiating our position that observed differences in ADCC do not play a clinically meaningful role in the potency of infliximab's mechanism of action (MoA) for the proposed clinical indications. However, in order to provide 'an adequate justification, including an evaluation of the role of ADCC particularly in the setting of inflammatory bowel disease', CELLTRION would like to ask FDA:*

- a. *In which specific aspects were the justifications submitted in the initial BLA not acceptable, or considered inadequate?*

### **FDA Response**

As stated previously, the results of your statistical testing should support that CT-P13 and US-licensed Remicade NK cell-dependent ADCC and FcγRIIIa binding are highly similar. The justifications provided in the original BLA did not provide adequate evidence to support that NK cell-dependent ADCC and FcγRIIIa binding are highly similar between CT-P13 and US-licensed Remicade.

We have recommended that NK cell-dependent ADCC be evaluated using Tier 2 quality range testing. We are also recommending that FcγRIIIa binding be evaluated using an appropriate statistical approach. Data from your testing of the reference product should be used to determine the acceptance criteria to support a demonstration that the products are highly similar.

However, if the results of your statistical testing of these attributes despite the addition of more lots are outside the pre-specified acceptance criteria, you may consider at that time providing updated literature and all in-house data to justify that the observed differences do not preclude a demonstration of highly similar. The adequacy of this justification, along with the proposal and demonstration of an appropriate control strategy, will be a review issue.

With respect to your proposal to address the differences in the ADCC assay in the context of extrapolation to all indications, we have the following comments: We have reviewed your “Position Paper on the Extrapolation of CT-P13 Data to Indications for which Licensure is Sought”. We understand that you believe that TNF sequestration is the primary function for infliximab, and that reverse signaling is the primary Fc-based function in IBD. We also understand that you contend that ADCC plays a minimal role in infliximab efficacy in IBD.

We believe that some key observations in the medical literature were not addressed. These observations could lead to alternative conclusions regarding the role of Fc effector functions (including ADCC) in the mechanism of action of anti-TNF therapies in the setting of IBD.

Specifically, you contend that the activity of TNF blockers with reduced or absent Fc function still possess efficacy in IBD. You cite certolizumab pegol (Cimzia, a pegylated humanized Fab’ fragment that lacks an Fc component) as effective for IBD treatment, implying that Fc effector functions (including ADCC) are not required for the clinical activity of TNF blockers, including infliximab, in this group of patients. However, you did not address other relevant data in the scientific literature:

- I. Although approved for use as a maintenance therapy for Crohn’s disease, clinical trials to demonstrate efficacy of certolizumab pegol in inducing remission in Crohn’s disease did not reach statistical significance (Sandborn et al, NEJM, 2007 and Sandborn et al, Clinical Gastroenterology and Hepatology, 2011). However, Cimzia did demonstrate statistically significant remission in Crohn’s disease at Week 26 vs. placebo in two separate studies, as described in the Cimzia USPI. In the absence of randomized data between certolizumab and infliximab, and taking into account the differences seen in the activity of certolizumab in IBD, there may be some differences in clinical response between certolizumab pegol and the anti-TNF mAbs, and thus ADCC cannot be ruled out

as a contributory factor to efficacy in IBD. A discussion of these points should have been included in the position paper.

- II. Several TNF-alpha blockers lacking or having attenuated Fc function have failed clinical trials for the Crohn's disease indication, arguing for the importance of intact Fc function for efficacy in IBD. These cases were omitted from the position paper. Several examples are included below.
- a. Etanercept, an Fc-TNFRp75 fusion protein (lacking the CH1 domain), failed to show any clinical response in active Crohn's disease (Sandborn et al, Gastroenterology, 2001). It should be noted that Etanercept has been shown to be capable of inducing ADCC *in vitro*, albeit, at a reduced level compared to Remicade (Mitoma et al, Arthritis & Rheumatism, 2008) (Arora et al, Cytokine 2009)
  - b. CDP571, an intact IgG4 targeting TNF $\alpha$ , failed to induce a statistically significant long term clinical response in moderate to severe Crohn's disease (Sandborn et al, Gut, 2004). Human IgG4 antibodies, while structurally similar to IgG1 antibodies like infliximab, differ in that they possess low ADCC inducing activity (Murphy, Janeway's Immunobiology 8<sup>th</sup> ed, 2012).
  - c. Onercept, a soluble TNFRp55 receptor protein, failed to induce remission in patients with active Crohn's disease (Rutgeerts et al, Clinical Gastroenterology and Hepatology, 2006).
- b. *What additional discussion of factors or elements already included in dossier Section 5.3.5.4 and additional Information Request (IR) responses does FDA expect to be included in the 'adequate justification, including an evaluation of the role of ADCC particularly in the setting of inflammatory bowel disease, that the observed difference in ADCC is not relevant to clinical activity'?*

#### **FDA Response**

Refer to FDA's response to Question 5a. You should address the comments provided in the response to Question 5a, comments (I) and (II) as an appendix to a revised "Position Paper on the Extrapolation of CT-P13 Data to Indications for which Licensure is Sought".

- c. *What additional factors or elements NOT previously included in dossier Section 5.3.5.4 and in IR responses does FDA expect to be considered and included in the 'adequate justification, including an evaluation of the role of ADCC particularly in the setting of inflammatory bowel disease, that the observed difference in ADCC is not relevant to clinical activity'?*

#### **FDA Response**

See responses to Questions 5a and 5b.

## **SAFETY UPDATE**

### **Question 6**

*CELLTRION would like to clarify the extent and the format of the safety update to be included in the BLA resubmission. Does FDA agree with the proposed plan for the safety update outlined in this briefing document?*

### **FDA Response**

Your proposal is reasonable. We also recommend including tables specific for adverse events of special interest.

## **IMMUNOGENICITY**

### **Question 7**

*For comment #1 relating to the immunogenicity seen in the healthy volunteer PK study, CELLTRION has conducted a root cause analysis to determine if there are any systematic reasons for the observations in the study. None were identified. The rationale supporting similarity of immunogenicity profiles of CT-P13 and US-licensed Remicade® rely on the totality of evidence in the program. We acknowledge that CT-P13 1.4 was the only study that used US-licensed Remicade®, and will further justify the rationale given in the initial BLA (Module 5, Section 5.3.5.4, Report on Immunogenicity Results from CT-P13 1.4 Study) and subsequent IR responses (SN0027 and SN0031). However, in order to provide ‘a rationale for why the results from study CT-P13 1.4 are in alignment with the conclusion that the immunogenicity profiles of CT-P13 and US-licensed Remicade® are similar’ CELLTRION would like to ask FDA if there are any additional factors or elements FDA consider important and pertinent to include in this rationale.*

### **FDA Response**

If biophysical differences (i.e. subvisible particulates) are ruled out as a cause for the observed differences between CT-P13 and US-licensed Remicade, the immunogenicity data generated using EU-approved infliximab could be used to address the residual uncertainty regarding immunogenicity. This would support a demonstration of no clinically meaningful differences between US-licensed Remicade and CT-P13 in terms of immunogenicity, assuming an adequate scientific bridge is provided.

## **STABILITY DATA**

### **Question 8**

*For comment #2 in regards to the stability data to support CT-P13 expiry date, CELLTRION wishes to clarify that the 36-57 months of stability data were submitted for the Process B DS batches manufactured by different DP manufacturing sites as part of the BLA amendment on 31 March 2015 (Section 3.2.P.8.3, from Table 3.2.P.8.3-1 to Table 3.2.P.8.3-12). Could FDA clarify whether:*

- a. *FDA expects DP shelf-life to be based on stability data from DP lots manufactured using Process B DS material?*
- b. *DP stability data (DP lots manufactured with Process B DS) from all DP manufacturing sites can be used to support the proposed shelf-life of CT-P13 DP?*
- c. *If not, could FDA clarify which DP site lots (manufactured using Process B DS) may be used to support CT-P13 shelf-life claim?*

### **FDA Response**

Our statement that current DP stability data using Process B batches of CT-P13 DS support an expiry date of 42 months, not (b) (4) months, was based on data submitted from drug product produced in Celltrion (b) (4) months as of time of review (b) (4) supported by the batches produced at other facilities (i.e., Rentschler, Binex).

Stability data from batches produced at commercial sites are considered to be conclusive for expiry claims. Stability data from pilot sites are considered supportive from the standpoint of (b) (4).

## **REGULATORY**

### **Question 9**

*The resubmission covering responses and supporting data for all the deficiencies noted in the CR letter is planned to be submitted by the end of August, 2015. It is CELLTRION's understanding that the BLA review can proceed focusing on the issues raised in the CR letter and that the original submission will not be re-reviewed nor the previously resolved issues will be brought up for further resolution unless the resubmitted data triggers such a review. Does FDA agree with this understanding? Does FDA also confirm that the resubmission will be subject to a six-month review clock?*

### **FDA Response**

The review of your resubmission will be focused on your responses to the deficiencies and comments articulated in the CR letter and the supporting data you submit. However, this information will be reviewed in the context of the totality of the evidence submitted as a part of your 351(k) BLA. Therefore, as part of this review, we may revisit already reviewed information that is relevant to the issues.

The timing of the review clock is subject to the adequacy of your complete response. However, if the resubmission constitutes a complete response addressing all the deficiencies outlined in the CR letter, we agree that per BsUFA it will be subject to a six-month review clock.

### **Question 10**

*CELLTRION assumes FDA will still seek advice from the Arthritis Advisory Committee, which has a tentative meeting date of October 23, 2015. Assuming CELLTRION resubmits the BLA by*

*August 2015, will FDA consider inclusion of CELLTRION's BLA for that meeting? If not, what is the earliest expected date for the Advisory Committee meeting? Assuming all major issues from the CR letter are resolved during the first half of the six-month clock, will the Advisory Committee meeting occur within the second half of the review clock?*

### **FDA Response**

At this time, FDA cannot provide additional information regarding the timing of an Advisory Committee meeting. The scheduling of an Advisory Committee meeting would depend on multiple factors, including the timing of your submission, the adequacy of the data submitted, and the time needed to prepare for such a meeting.

### **Additional Comment**

In your "Position Paper on the Extrapolation of CT-P13 Data to Indications for which Licensure is Sought" (page 151), you state that you plan to perform a clinical study comparing CT-P13 and US-licensed Remicade in Crohn's Disease patients. Please describe the timeframe of completion of this clinical study and provide a summary of the design.

## **3. ADDITIONAL INFORMATION**

### **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 (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team ([cdcr-edata@fda.hhs.gov](mailto:cdcr-edata@fda.hhs.gov)) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page 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.

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 start 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 Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

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/s/  
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PHUONG N TON  
08/04/2015



BLA 125544

**MEETING REQUEST GRANTED**

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

Attention: Sally Choe, PhD  
Senior Director, Parexel International

Dear Dr. Choe:

Please refer to your Biologic License Application (BLA) submitted under section 351(k) of the Public Health Service Act for CT-P13.

We also refer to your June 19, 2015, correspondence requesting a meeting to discuss the deficiencies identified in the Complete Response Letter and the resubmission of the BLA. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Biosimilar Biological Product Development (BPD) Type 1 Meeting.

The meeting is scheduled as follows:

**Date:** August 5, 2015  
**Time:** 1:00 – 2:00 PM EST  
**Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room 1311  
Silver Spring, Maryland 20903

**Invited CDER participants:**

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)  
Sarah Yim, MD, Supervisory Associate Director, DPARP  
Nikolay Nikolov, MD, Clinical Team Leader, DPARP  
Juwaria Waheed, MD, Clinical Reviewer, DPARP  
Timothy Robison, PhD, Pharmacology/Toxicology Supervisor, DPARP  
Matthew Whittaker, PhD, Pharmacology/Toxicology Reviewer, DPARP  
Ping Ji, PhD, Acting Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)  
Lei He, PhD, Clinical Pharmacology Reviewer, DCPII, OCP  
Ruthanna Davi, PhD, Deputy Director, Division of Biometrics II, Office of Biostatistics (OB)  
Gregory Levin, PhD, Biostatistics Team Leader, Division of Biometrics II, OB

Yi Tsong, PhD, Division Director, Division of Biometrics VI, Office of Biostatistics (OB)  
Meyiu Shen, PhD, Team Leader, Division of Biometrics VI, Office of Biostatistics (OB)  
Steven Kozolwski, MD, Director, Office of Biotechnology Products (OBP), Office of  
Pharmaceutical Quality (OPQ)  
David Frucht, MD, Acting Director, Divisions of Biotechnology Review and Research II  
(DBRRII), OBP, OPQ  
Kurt Brorson, PhD, Laboratory Chief, DBRRII, OBP, OPQ  
Peter Adams, PhD, Senior Staff Fellow, DBRRI, OBP, OPQ  
Marlene Schultz-DePalo, MS, MA, RAC, Biosimilar Program and Policy Analyst, OBP,  
OPQ  
Leah Christl, PhD, Associate Director for Therapeutic Biologics, Therapeutic Biologics and  
Biosimilars Staff (TBBS)  
Sue Lim, MD, Senior Staff Fellow, TBBS  
Carla Lankford, MD, PhD, Science Policy Analyst, TBBS  
Neel Patel, PharmD, Regulatory Project Manager, TBBS  
Tyree Newman, Senior Regulatory Health Project Manager, TBBS  
Janice Weiner, JD, MPH, Senior Regulatory Counsel, Division of Regulatory Policy I (DRP  
I), Office of Regulatory Policy (ORP)  
David Kettl, MD, Clinical Team Leader, Division of Dermatology and Dental Products  
Jessica Lee, MD, Medical Officer, Division of Gastroenterology and Inborn Errors Products  
Juli Tomaino, MD, Medical Officer, Division of Gastroenterology and Inborn Errors  
Products  
Nina Ton, PharmD, Senior Regulatory Project Manager, DPARP

Please e-mail me any updates to your attendees at [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Nina Ton at 301-796-1648; Division Secretary at 301-796-2300.

If the materials presented in the meeting package are inadequate to prepare for the meeting, we may cancel or reschedule the meeting

If you have any questions, call me at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Nina Ton, PharmD  
Senior Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

## FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	August 5, 2015; 1:00 PM
MEETING ENDING DATE AND TIME	August 5, 2015; 2:00 PM
PURPOSE OF MEETING	BPD Type 1 Meeting
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	White Oak Building 22, Conference Room 1311
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Nina Ton Senior Regulatory Project Manager WO22, Room 3311 301-796-1648
ESCORT INFORMATION (If different from Hosting Official)	

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/s/  
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PHUONG N TON  
07/01/2015



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** May 27, 2015

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 Information Request

Total no. of pages including  
cover and signature page 3

**Comments:** Please acknowledge receipt

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Document to be emailed to: Sally.Choe@parexel.com

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**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

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BLA 125544  
CT-P13  
Celltrion, Inc.

Dear Dr. Choe:

We are reviewing your submission dated August 8, 2014, and have the following request for information.

Submit an amendment to your 351(k) BLA to include information found in the “action package” for the Remicade BLA (see draft guidance on Biosimilars: Additional Questions and Answers Regarding Implementation of the BPCI Act, Q+A I.13). For your convenience, your amendment may provide a Web link to the Summary Basis of Approval and FDA reviews currently available at [Drugs@FDA](mailto:Drugs@FDA), accompanied by a list of the documents that you intend to reference (identified by title and date), and this information will be incorporated by reference into your 351(k) BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/May 27, 2015  
Cleared by: TBBS/ORP/May 27, 2015  
LJafari/May 27, 2015  
Finalized by: NTon/May 27, 2015

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/s/  
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PHUONG N TON  
05/27/2015

**PeRC Meeting Minutes**  
**April 29, 2015**

**PeRC Members Attending:**

Lynne Yao (Chair for all products through (b) (4))

Robert "Skip" Nelson

Wiley Chambers

Rosemary Addy

George Greeley

Frede Crooner

Tom Smith

Karen Davis-Bruno

Daiva Shetty

Andrew Mulberg (b) (4)

Greg Reaman (b) (4)

Barbara Buch

Adrienne Hornatko-Munoz

Barbara Buch

Andrew Mosholder (b) (4)

Hari Cheryl Sachs

Julia Pinto

Lily Mulugeta

Olivia Ziolkowski

Kevin Krudys

Rachel Witten

Dianne Murphy

Maura O'Leary

Kristiana Brugger (b) (4)

**Agenda**

NON-RESPONSIVE

11:40	BLA	125544	CT-P13 (Biosimilar) Partial Waiver/Assessment) *Agreed iPSP*	All approved adult indications and Pediatric Ulcerative Colitis and Pediatric Crohn's Disease
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NON-RESPONSIVE

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NON-RESPONSIVE

**CT-P13 (Biosimilar to Remicade (infliximab)) Partial Waiver/Assessment**

- Proposed Indication: All approved adult indications and Pediatric Ulcerative Colitis and Pediatric Crohn's Disease
- DPARP noted that the central issue with the proposed biosimilar is the preferred change in the age group for waiver of studies in children for pediatric Crohn's Disease. Products previously approved for pediatric Crohn's Disease included a waiver of pediatric studies in patients below six years of age but a change in thinking within the Division has led to a preferred waiver in patients less than two years of age. Proceeding with a waiver in patients less than two years of age would essentially not allow the biosimilar to continue on the 351K pathway.
- DGIEP would be agreeable and allow an exception for biosimilar products for previously approved innovator products to reflect a pediatric waiver in patients less than 6 years of age because of the current label of the referenced product. However, all new products submitted to the Agency moving forward will be required to conduct pediatric studies in patients two years of age and older.
- DGIEP noted that a consult has been submitted to OSE for pediatric use data for infliximab.
- It was also noted that NON-RESPONSIVE product would be allowed to follow the

current labeling and would include a waiver in patients less than six years of age for pediatric Crohn's Disease.

- PeRC Recommendations:
  - The PeRC agreed with the Division plan for a partial waiver and assessment. In particular, the partial waiver for Crohn's Disease in pediatric patients ages birth to 6 years based on the current labeling of the referenced product. Any new products submitted to the Agency for this indication would be subject to PREA requirements to study patients down to 2 years of age.

NON-RESPONSIVE

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/s/  
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GEORGE E GREELEY  
05/14/2015



BLA 125544

**DEFICIENCIES PRECLUDE DISCUSSION**

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

Attention: Sally Choe, PhD  
Senior Director, Parexel International

Dear Dr. Choe:

Please refer to your Biologics License Application (BLA) dated August 8, 2014, received August 8, 2014, submitted under section 351(k) of the Public Health Service Act for CT-P13.

We also refer to our October 21, 2014, letter in which we notified you of our target date of May 11, 2015, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the “Biosimilar Biological Product Authorization Performance Goals and Procedures for Fiscal Years 2013 Through 2017.”

As part of our ongoing review of your application, we have identified deficiencies that preclude discussion of labeling and postmarketing requirements/commitments at this time.

This notification does not reflect a final decision on the information under review.

If you have any questions, call Nina Ton, Regulatory Project Manager, at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Ladan Jafari  
Chief, Project Management Staff  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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LADAN JAFARI  
05/06/2015



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

---

**Date:** April 10, 2015

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 CMC Information Request

Total no. of pages including  
cover and signature page 3

**Comments:** Please acknowledge receipt and respond by April 17, 2015

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Document to be emailed to: Sally.Choe@parexel.com

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BLA 125544  
CT-P13  
Celltrion, Inc.

Dear Dr. Choe:

We are reviewing your submission dated August 8, 2014, and have the following requests for information:

Provide an update regarding the status and timeline for addressing of close-out recommendations discussed at the end of the Celltrion facility inspection on March 6, 2015. We recommended that the close out recommendations be address in an amendment to the BLA. The recommendations were:

1. Regarding the Identity assay after DP labeling, we recommended a highly product specific assay such as tryptic peptide mapping be used. An assay should possess an unique and unambiguous pattern from each of the Abs under development/manufactured at Celltrion's facility (or other DP manufacturing sites). Considering future product development, an assay that is suitable now may not be adequate later if several more antibodies are added to the pipeline.
2. A modified visible particle assay should be developed and implemented as described during discussions at the inspection site. The revised assay should test a suitable number of replicate vials. A comparison between US-licensed Remicade and CT-P13 in infusion bags should be performed as well.
3. A plan for tighter specifications for glycans as measured by HPAEC-PAD method or strong justification why the FcγRIIIa SPR assay is an adequate substitute for tighter specifications should be submitted.

In order to facilitate the review of your submission, provide the requested information no later than April 17, 2015. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/April 10, 2015  
Cleared by: KBrorson/April 10, 2015  
LJafari/April 10, 2015  
TBBT/April 10, 2015  
Finalized by: NTon/April 10, 2015

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/s/  
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PHUONG N TON  
04/10/2015



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

---

**Date:** April 7, 2015

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 CMC Information Request

Total no. of pages including  
cover and signature page 3

**Comments:** Please acknowledge receipt and respond by April 14, 2015

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Document to be emailed to: Sally.Choel@parexel.com

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BLA 125544  
CT-P13  
Celltrion, Inc.

Dear Dr. Choe:

We are reviewing your submission dated August 8, 2014, and have the following request for information. Submit the following study results for our further assessment of immunogenicity:

- The immunogenicity results using ECLA assay for study CT-P13 1.4.

In order to facilitate the review of your submission, provide the requested information no later than April 14, 2015. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/April 3, 2015  
Cleared by: LHe/April 2, 2015  
              Pji/April 2 and 6, 2015  
              LJafari/April 3, 2015  
              TBBT/April 3 and 6, 2015  
Finalized by: NTon/April 7, 2015

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/s/  
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PHUONG N TON  
04/07/2015



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** April 1, 2015

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 CMC Information Request

Total no. of pages including  
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**Comments:** Please acknowledge receipt and respond by April 15, 2015

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BLA 125544  
CT-P13  
Celltrion, Inc.

9. Provide the results for the studies Celltrion committed to conduct in the amendment dated February 24, 2015 (Sequence 24), namely the [REDACTED] (b) (4) [REDACTED] validation.

In order to facilitate the review of your submission, provide the requested information no later than April 15, 2015. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/March 27, 2015  
Cleared by: BChi/March 27 and 31, 2015  
PHughes/March 27 and 31, 2015  
LJafari/March 27, 2015  
TBBT/March 31, 2015  
Finalized by: NTon/April 1, 2015

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/s/  
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PHUONG N TON  
04/01/2015



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** March 20, 2015

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 Review Comments

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Document to be emailed to: Sally.Choe@parexel.com

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BLA 125544  
CT-P13  
Celltrion, Inc.

Dear Dr. Choe:

We are reviewing your submission dated August 8, 2014, and your March 9, 2015, response to our information request dated February 13, 2015. We have the following comments.

In your proposal, each lot contributes many independent observations so the within-lot variability can be estimated. We do not agree with your proposal. We recommend that you re-analyze your data using the approach described below (one value per lot).

In this recommended approach, contribution of the within-lot variability (including assay variability) can be minimized if multiple replicates are obtained, and the average of the replicates is subsequently reported as one value per lot. By minimizing within-lot variability, lot-to-lot variability is the main concern since the test is a comparison of means between the reference product (US-licensed Remicade) and the proposed biosimilar product. Including a sufficient number of US-licensed Remicade and proposed biosimilar lots in your similarity exercise can help address lot-to-lot variability.

Furthermore, with respect to ADCC you pooled the results obtained from performing the assay using three different antibody concentrations. We do not agree with combining data from the different levels, we recommend comparing the lot means between CT-P13 and US-licensed Remicade at each concentration level.

You also proposed a mean (b) (4) testing. This is not acceptable. We recommend that you re-analyze your data using  $\pm x\sigma_{ref}$  which already includes  $\pm \sigma_{ref} / 8$ .

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/March 19, 2015  
Cleared by: MShen/March 19 and 20, 2015  
              YTsong/March 19, 2015  
              LJafari/March 19, 2015  
              TBBT/March 19 and 20, 2015  
Finalized by: NTon/March 20, 2015

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/s/  
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PHUONG N TON  
03/20/2015



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** February 27, 2015

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 CMC Information Request

Total no. of pages including  
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**Comments:** Please acknowledge receipt and respond by March 6, 2015

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Document to be emailed to: Sally.Choe@parexel.com

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Dear Dr. Choe:

We are reviewing your submission dated August 8, 2014, and have the following comments and requests for information:

1. You provided the results of a 3-way PK study conducted in healthy volunteers (CT-P13 1.4). We note that many of the samples collected in the course of the study had levels of circulating drug exceeding the drug tolerance levels defined for your anti-drug antibody (ADA) screening assay (i.e., 10 µg/mL, 10 µg/mL, and 5 µg/mL for CT-P13, US-licensed Remicade, and EU-approved infliximab, respectively). The presence of circulating drug levels above the drug tolerance levels may affect the interpretation of the ADA immunogenicity data in the study. Provide a table listing the circulating drug levels for each patient at the time of ADA sampling for Study CT-P13 1.4 and the corresponding ADA titers. This table should include the circulating drug levels at the time of sampling, the positive or negative result from the screening assay, the sample ADA titer, the positive or negative result from the neutralizing assay result, and the neutralizing assay titer. Provide the table in an Excel format if possible. Additionally, clarify why the drug tolerance level for EU-approved infliximab is different than those for US-licensed Remicade and CT-P13.
2. The results of Study CT-P13 1.4 indicate that the percent of samples that screened ADA positive in subjects treated with US-licensed Remicade is lower than the percent of samples that screened ADA positive in subjects treated with EU-approved infliximab and CT-P13. Provide a rationale for this difference in the percentage of screened ADA positive samples observed in the study.
3. You submitted SOP (b)(4) Job Number 181548 for the ELISA method used to analyze samples collected in Study CT-P13 1.4. The SOP states that ADA samples are acidified to dissociate excess study drug from the ADA in serum samples. However, the validation report you provided does not include validation of the acidification step. Clarify whether the acidification step was performed for the samples collected in Study CT-P13 1.4 and provide your rationale for the inclusion or exclusion of this step in the sample assessment. If acidification was performed in the assay, provide validation data demonstrating that the acidification procedure effectively increases the sensitivity of the screening assay.
4. The Immunoassay Sample Analysis Report (b)(4) Job Number 181549, Amendment 1) states that samples from Study CT-P13 1.4 will be retained for at least (b)(4).
  - i. Confirm that the samples are currently available and have been maintained at (b)(4).
  - ii. Comment on the amount of samples retained and the feasibility of performing additional analysis on the retained samples.
  - iii. Clarify whether any serum samples were taken from patients after Day 57 in Study CT-P13 1.4 that could potentially be used for additional immunogenicity testing.

BLA 125544  
CT-P13  
Celltrion, Inc.

In order to facilitate the review of your submission, provide the requested information no later than March 6, 2015. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/February 26, 2015  
Cleared by: WHallett/February 26 and 27, 2015  
HDickensheets/February 26 and 27, 2015  
LJafari/February 26, 2015  
TBBT/February 26, 2015  
Finalized by: NTon/February 27, 2015

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/s/  
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PHUONG N TON  
02/27/2015



BLA 125544

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Sally Choe, PhD  
Senior Director

Dear Dr. Choe:

Please refer to your Biologics License Application (BLA) dated and received August 8, 2014, submitted under section 351(k) of the Public Health Service Act for CT-P13.

We also refer to your November 27, 2014, correspondence, received November 28, 2014, requesting review of your proposed proprietary name, Inflectra, for CT-P13, a proposed biosimilar to US-licensed Remicade (Infliximab).

We have completed our review of the proposed proprietary name, Inflectra and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your November 27, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sarah Harris, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4774. For any other information regarding this application, contact Nina Ton, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Deputy Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES  
02/23/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 118135  
BLA 125544/0

**PROPRIETARY NAME REQUEST  
WITHDRAWN**

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

ATTENTION: Sally Choe, PhD  
Senior Director

Dear Dr. Choe:

Please refer to:

- your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CT-P13 and
- your Biologics License Application (BLA) dated and received August 8, 2014, submitted under section 351(k) of the Public Health Service Act for CT-P13.

We also refer to:

- your correspondence dated and received May 20, 2014, requesting review of your proposed proprietary name, (b) (4) for your IND; and
- your correspondence, dated and received September 26, 2014, requesting review of your proposed proprietary name, (b) (4) for your 351(k) BLA; and
- your correspondence dated and received February 10, 2015, requesting withdrawal of your proposed proprietary name, (b) (4)

This proprietary name request is considered withdrawn as of February 10, 2015.

We note that you have proposed an alternate proprietary name in your submission dated November 27, 2014, and received November 28, 2014. The review of your proposed alternate name, Inflectra, has been initiated.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sarah Harris, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4774. For any other information regarding this application, contact Nina Ton, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Sarah Harris, PharmD  
Safety Regulatory Project Manager  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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SARAH J HARRIS  
02/17/2015



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

---

**Date:** February 13, 2015

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 CMC Information Request

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**Comments:** Please acknowledge receipt and respond by February 27, 2015

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Document to be emailed to: Sally.Choe@parexel.com

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Dear Dr. Choe:

We are reviewing your submission dated August 8, 2014, and have the following comments and requests for information:

1. Fucosylation is an important attribute of CT-P13, because the degree of fucosylation affects binding of CT-P13 to FcγRIIIa and its effector function. We note that the data you provided in your submission are inconsistent in regard to fucose level in CT-P13, US-licensed Remicade and EU-approved infliximab. In table 3.2.R-124, you provided an estimate of the total proportion of afucosylated species by HPAEC-PAD. The data provided in the table show that EU-approved infliximab has higher fucosylation levels than CT-P13. These findings contrast data from Table 3.2.R-25 showing fucose levels obtained by summing Man5 and G0 levels from an oligosaccharide profiling assay. The data provided in this table indicate that fucose levels are similar in CT-P13, US-licensed Remicade and EU-approved infliximab. Moreover, Table R-126 shows a monosaccharide analysis where fucosylation is similar in CT-P13, US-licensed Remicade and EU-approved infliximab.
  - a. Provide an explanation for the inconsistencies in the fucosylation results and a detailed description of each of the three assays used to generate data depicted in the three tables. In addition, clearly indicate the purpose of each assay.
  - b. Provide a scientific rationale to justify that summing the amount of Man5 and G0 glycans will give an accurate estimate of afucosylation, as was performed in table R-25. Clarify which glycan nomenclature system you are using. Clarify why other glycans typically present on antibodies, such as G1 or Man6 were not included in the calculation. Justify why this method is used instead of the HPAEC-PAD as in the two-way analysis.
2. Protein content uniformity is a critical quality attribute for CT-P13, because it ensures that patients receive a consistent dosage of the product. You measured protein concentration using the molar extinction coefficient. However, we have questions regarding these data as follows:
  - a. In your submission you included the results of the amino acid analysis and also determined the molar absorptivity (extinction coefficient) for each product lot as shown in Table 3.2.R-9. We note that the data obtained from the amino acid analysis of CT-P13, while largely matching those of US-licensed Remicade, differed in that tyrosine (Tyr) values were lower, and generally more variable, than the values obtained for both EU-approved infliximab and US-licensed Remicade. Moreover, the Tyr value from the analysis of CT-P13 lot 12B1C016 was significantly less than the two other lots of CT-P13 (12B1C015 and 12B1C017). We further note that the values obtained for the molar absorptivity of the three CT-P13 lots reported in this table are higher than those obtained

for both the EU-approved infliximab and US-licensed Remicade. To address these concerns, we have the following requests:

- i. Provide a scientific explanation for the discrepancy in the Tyr data between CT-P13 and US-licensed Remicade. Address whether this is due to assay method or if it reflects a true difference in amino acid content/sequence. Clarify whether the CT-P13 and US-licensed Remicade test articles were tested side-by-side or on different days.
  - ii. Explain the variability in Tyr values between different lots of CT-P13. If an explanation is not available, we recommend that additional lots be tested by amino acid analysis to establish the range and average value of Tyr.
- b. Provide a step-by-step description of the procedure and calculation used to conduct the amino acid analysis in Table 3.2.R-9, as well as the procedure and calculation used to determine the extinction coefficients
- i. Address whether the acid-based amino acid liberation procedure that you used in your assay could damage individual amino acids like Tyr or Trp.
  - ii. Provide the equation of how these data were subsequently used to calculate the concentrations of US-licensed Remicade and CT-P13 Drug Product.
  - iii. In section 3.2.R.5.1.5 you state that “The derivations of the molar absorptivity values were performed using the previously mentioned robust amino acids”. This list did not include Tyrosine or Tryptophan, which are generally considered to be the amino acids that contribute the most to protein absorptivity and extinction coefficients. Explain why this procedure was used if the absorptivity contribution of these two amino acids are not included in the final calculation of the extinction coefficient.
  - iv. Provide a scientific explanation for the apparent difference in protein concentrations between U.S-licensed Remicade and CT-P13. Specifically address whether this difference could be explained by differences in your experimentally determined extinction coefficients.
    - 1) Clarify whether you used one unified extinction coefficient to determine protein concentrations for all lots in your 3-way analysis, or whether you used experimentally-derived extinction coefficients, which vary between CT-P13, US-licensed Remicade and EU-approved infliximab.
  - v. Describe current measures taken to match CT-P13 protein content to US-licensed Remicade.

- vi. If further analysis reveals that the CT-P13 and US-licensed Remicade protein contents actually are consistently 3-4% different, describe plans to readjust the CT-P13 (b) (4) process to allow its protein content to more closely match that of US-licensed Remicade.
  - vii. If protein content/concentration values of individual lots of US-licensed Remicade, EU- approved infliximab or CT-P13 require readjustment after re-analysis of the product extinction coefficients, we recommend statistical reanalysis of all assays where results are expressed as units per mg antibody (e.g., binding assays like FcRn, etc.).
  - viii. Address whether additional lots of US-licensed Remicade, EU-approved infliximab and CT-P13 are available to compare protein content with a more representative number of batches.
    - 1) We recommend using reference lots covering various expiration periods to avoid clustering data from related lots.
    - 2) Address whether clinical batches are available for this purpose.
3. The binding of TNF- $\alpha$  is a critical component of the mechanism of action of CT-P13, and in a risk ranking assessment, TNF- $\alpha$  binding is high in criticality ranking. Therefore, a wider range of lots should be analyzed by a statistical equivalency test for TNF- $\alpha$  binding. The results of the statistical equivalency test conducted by the FDA showed that the EU-approved-infliximab did not meet the equivalency margins established based on analysis of US-licensed Remicade for this parameter. We believe that this result might be due to the limited number of lots you provided in your submission. Provide additional data on TNF binding assay for available lots of CT-P13, EU-approved infliximab and US-licensed Remicade.
4. The power of statistical analyses presented in section 3.2.R appears compromised by using data from a limited number of batches. In your Table 3.2.R-2, you listed 13 batches available for your three 3-way similarity studies (denoted “Initial IND, Abridged”, “IND amendment, Enhanced study”, “BLA, Statistical powering”). We note that not all 13 batches are used for all quality attributes. For example, you provided protein content data from the 10 batches denoted “Abridged study” and “Enhanced study”; and TNF Binding Affinity (ELISA) data from 10 batches denoted “Enhanced study” and “Statistical powering study”. SEC-HPLC, SEC-MALS, AUC, CE-SDS used lots only denoted “Abridged study” and “Enhanced study”. In addition, we note that there is no analytical data from 2 US-licensed Remicade clinical batches and 2 EU-approved infliximab clinical batches.

BLA 125544  
CT-P13  
Celltrion, Inc.

- a. To perform a more powerful statistical analysis, provide analytical data of all 13 batches for all quality attributes.
- b. The statistical analysis would also be improved if the analytical data of the 2 US-licensed Remicade batches and 2 EU-approved infliximab batches used in the Celltrion clinical studies were used and provided.

In order to facilitate the review of your submission, provide the requested information no later than February 27, 2015. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/February 12, 2015  
Cleared by: PAdams/February 12, 2015  
KBrorson/February 12 and 13, 2015  
DFrucht/February 12, 2015  
SKozlowski/February 12, 2015  
LJafari/February 13, 2015  
TBTT/February 13, 2015  
Finalized by: NTon/February 13, 2015

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/s/  
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PHUONG N TON  
02/13/2015

## Harris, Sarah

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**From:** Harris, Sarah  
**Sent:** Monday, February 09, 2015 3:00 PM  
**To:** 'Seiler, Jennifer'  
**Cc:** Choe, Sally  
**Subject:** RE: BLA 125544 Request for Proprietary Name Teleconference

**Follow Up Flag:** Follow up  
**Flag Status:** Flagged

**Categories:** DPARP

Hi Jennifer,

Thank you for providing a list of attendees at this morning's teleconference. A list of FDA attendees is below.

In response to your inquiries:

- 1) Clearly note on your cover letter that you are requesting to withdraw the proposed proprietary name "(b) (4) Your proposal for wording is acceptable.
- 2) Please submit this request to both BLA 125544 and IND 118135.
- 3) In the letter to the BLA, please reference your submission requesting review of the proposed proprietary name "Inflectra", and indicate that "Inflectra" is your preferred name for CT-P13.

FDA Attendees:

Kellie Taylor, PharmD, MPH, Deputy Director, OMEPRM  
Todd Bridges, RPh, Deputy Director, DMEPA  
Lubna Merchant, MS, PharmD, Associate Director, DMEPA  
Kendra Worthy, PharmD, Team Leader, DMEPA  
Teresa McMillan, PharmD, Safety Evaluator, DMEPA  
Colleen Brennan, RPh, Workload Coordinator, DMEPA  
Sarah Harris, PharmD, Project Manager, OSE  
Sally Seymour, MD, Deputy Director for Safety, DPARP  
Carol Hill, MS, Safety Regulatory Project Manager, DPARP  
Tyree Newman, Project Manager, OND TBBT

Kind regards,  
Sarah

Sarah Harris, PharmD  
Safety Regulatory Project Manager | OSE | CDER | FDA  
[sarah.harris@fda.hhs.gov](mailto:sarah.harris@fda.hhs.gov) | 240.402.4774

---

**From:** Seiler, Jennifer [<mailto:Jennifer.Seiler@parexel.com>]  
**Sent:** Monday, February 09, 2015 10:27 AM

**To:** Harris, Sarah  
**Cc:** Choe, Sally  
**Subject:** RE: BLA 125544 Request for Proprietary Name Teleconference

Hi Sarah,

Thank you for meeting with us this morning. Below is a list of attendees from Celltrion/PAREXEL. Can you provide a list of attendees from FDA; we want to be sure we have captured everyone. Additionally, should we identify this as 'Withdrawal of proposed proprietary name [REDACTED] (b) (4)' in the cover letter? And this only needs to go to the BLA, and not the IND correct?

Kind regards,  
Jennifer

Attendees:

JaeHwee Park, Head Regulatory, Celltrion  
JooHee Lee, Assistant Manager Regulatory, Celltrion  
Jennifer Seiler, PAREXEL Consulting, US Agent Representative  
Renee Martin, PAREXEL Consulting, Regulatory/PM

**Jennifer A. Seiler, PhD, RAC**

Senior Consultant  
PAREXEL International  
T +1 301.634.8034  
F +1 301.634.8040  
M [REDACTED] (b) (6)

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**From:** Harris, Sarah [<mailto:Sarah.Harris@fda.hhs.gov>]  
**Sent:** Thursday, February 05, 2015 1:03 PM  
**To:** Seiler, Jennifer  
**Cc:** Choe, Sally  
**Subject:** RE: BLA 125544 Request for Proprietary Name Teleconference

Hi Jennifer,  
Thank you for confirming and providing the call-in number.

Kind regards,  
Sarah

---

**From:** Seiler, Jennifer [<mailto:Jennifer.Seiler@parexel.com>]  
**Sent:** Thursday, February 05, 2015 11:00 AM  
**To:** Harris, Sarah  
**Cc:** Choe, Sally  
**Subject:** RE: BLA 125544 Request for Proprietary Name Teleconference

Hi Sarah,

Thank you for your email and your request. Members of the team will be available at that time (2/9, 9:30AM). Please see dial-in information below.

Toll-free Dial-In: (b) (6)  
Conference code (b) (6)

Kind regards,  
Jennifer

**Jennifer A. Seiler, PhD, RAC**

Senior Consultant

PAREXEL International

T +1 301.634.8034

F +1 301.634.8040

M (b) (6)

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**From:** Harris, Sarah [<mailto:Sarah.Harris@fda.hhs.gov>]  
**Sent:** Wednesday, February 04, 2015 8:34 PM  
**To:** Seiler, Jennifer  
**Subject:** BLA 125544 Request for Proprietary Name Teleconference

Hi Jennifer,  
FDA would like to request a brief teleconference to discuss the additional proposed proprietary name Inflectra for CT-P13 submitted under BLA 125544. The Agency would like further clarification of the marketing intent of CT-P13 in the context of (b) (4).

We have preliminarily scheduled a time on Monday, February 9<sup>th</sup> from 9:30-10:00 AM EST.

Please confirm your availability for this time.

Kind Regards,  
Sarah

Sarah Harris, PharmD  
Safety Regulatory Project Manager | OSE | CDER | FDA  
[sarah.harris@fda.hhs.gov](mailto:sarah.harris@fda.hhs.gov) | 240.402.4774

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/s/  
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SARAH J HARRIS  
02/10/2015



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** February 6, 2015

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648
<b>Subject:</b> BLA 125544 CT-P13 CMC Microbiology Information Request	

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**Comments:** Please acknowledge receipt and respond by February 17, 2015

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Document to be emailed to: Sally.Choe@parexel.com

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Dear Dr. Choe:

We are reviewing your submission dated August 8, 2014, and your amendment dated December 26, 2014, which was in response to our information request correspondence dated December 10, 2014. We have the following comments and requests for information:

**1. Description of the Manufacturing Process and Process Controls – Batches and Scale Definition – Upstream Manufacturing Process and Process Controls:**

With regard to your response to question 1.d, amend the BLA to reflect the (b) (4) current (b) (4).

**2. Description of the Manufacturing Process and Process Controls – Batches and Scale Definition – Downstream Manufacturing Process and Process Controls**

With regard to your response to question 2.f, amend the BLA to reflect the change in the sampling points.

With regard to your response to question 2.k, clarify if (b) (4) raw material is tested for endotoxin and provide specifications; if the raw material is not tested, establish endotoxin specification for the (b) (4). In addition, justify why (b) (4).

**3. Process Validation and/or Evaluation – In-Process Hold Validation**

With regard to your response to question 5.b, provide the expected date when the results of the media hold study will be submitted to the Agency.

In order to facilitate the review of your submission, provide the requested information no later than February 17, 2015. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/February 4, 2015  
Cleared by: RCandau-Chacon/February 6, 2015  
PHughes/February 6, 2015  
LJafari/February 4, 2015  
TBBT/February 6, 2015  
Finalized by: NTon/February 6, 2015

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/s/  
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PHUONG N TON  
02/06/2015

## Harris, Sarah

---

**From:** Seiler, Jennifer <Jennifer.Seiler@parexel.com>  
**Sent:** Thursday, February 05, 2015 11:00 AM  
**To:** Harris, Sarah  
**Cc:** Choe, Sally  
**Subject:** RE: BLA 125544 Request for Proprietary Name Teleconference

**Categories:** DPARP

Hi Sarah,

Thank you for your email and your request. Members of the team will be available at that time (2/9, 9:30AM). Please see dial-in information below.

Toll-free Dial-In: (b) (6)  
Conference code: (b) (6)

Kind regards,  
Jennifer

### Jennifer A. Seiler, PhD, RAC

Senior Consultant  
[PAREXEL International](#)  
T +1 301.634.8034  
F +1 301.634.8040  
M (b) (6)

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**From:** Harris, Sarah [<mailto:Sarah.Harris@fda.hhs.gov>]  
**Sent:** Wednesday, February 04, 2015 8:34 PM  
**To:** Seiler, Jennifer  
**Subject:** BLA 125544 Request for Proprietary Name Teleconference

Hi Jennifer,  
FDA would like to request a brief teleconference to discuss the additional proposed proprietary name Inflectra for CT-P13 submitted under BLA 125544. The Agency would like further clarification of the marketing intent of CT-P13 in the context of (b) (4)

We have preliminarily scheduled a time on Monday, February 9<sup>th</sup> from 9:30-10:00 AM EST.

Please confirm your availability for this time.

Kind Regards,  
Sarah

Sarah Harris, PharmD  
Safety Regulatory Project Manager | OSE | CDER | FDA  
[sarah.harris@fda.hhs.gov](mailto:sarah.harris@fda.hhs.gov) | 240.402.4774

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SARAH J HARRIS  
02/05/2015



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** February 5, 2015

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648
<b>Subject:</b> BLA 125544 CT-P13 Statistics Information Request	

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Dear Dr. Choe:

We are reviewing your submission dated August 8, 2014, and have the following requests for information:

In your November 14, 2014, response to Question 3 of our information request (IR), you stated that “the difference in the number of patients with an assessment between initial and rereading results in Table 1 were mainly driven by full set of required joints for radiographic scoring found to be incomplete during the re-reading process.” Clarify what is meant by a “full set of required joints for radiographic scoring found to be incomplete,” as we have been unable to replicate the numbers of patients reported in that table. For example, consider the re-reading results for the all-randomized population. Below, we have summarized baseline and Week 54 results for all randomized patients in Study 3.1 who had nonmissing scores for every joint assessment for both readers at that particular visit (according to the adam.adjdpred dataset). While our results agree with those in Table 1 at Week 54, we identified many more patients at baseline with seemingly complete radiographic assessments.

	CT-P13	EU-Remicade
<b>Baseline</b>		
n	275	271
Mean (SD)	69.1 (60.9)	65.4 (61.8)
<b>Week 54</b>		
n	206	201
Mean (SD)	66.0 (58.4)	63.7 (59.9)

**Table 1: Comparison of Joint Damage Progression results in CT-P13 3.1 and ATTRACT studies**

Statistics	Study CT-P13 3.1						ATTRACT
	Initial results (Per-protocol)		Re-reading results (Per-protocol)		Re-reading results (All-randomized)		
	CT-P13 3 mg/kg (N=246)	EU-approved Remicade® 3 mg/kg (N=250)	CT-P13 3 mg/kg (N=246)	EU-approved Remicade® 3 mg/kg (N=250)	CT-P13 3 mg/kg (N=302)	EU-approved Remicade® 3 mg/kg (N=304)	
<b>Baseline</b>							
n	206	207	191	194	232	238	N/A
Mean (SD)	105.7 (68.18)	103.3 (67.77)	66.0 (57.30)	63.3 (59.98)	68.3 (58.88)	64.8 (62.46)	79.0 (73.0)
<b>Week 54</b>							
n	213	207	198	196	206	201	N/A
Mean (SD)	70.4 (56.91)	73.0 (60.68)	66.5 (58.60)	64.4 (60.48)	66.0 (58.38)	63.7 (59.93)	N/A
<b>Change From Baseline at Week 54</b>							
n	182	174	163	163	168	168	71
Mean (SD)	-32.5 (26.85)	-28.7 (30.66)	0.9 (5.97)	0.6 (5.42)	1.0 (6.25)	0.6 (5.56)	1.3 (6.0)

Source: CSR CT-P13 3.1 Post-text Table 14.2.6.3, Section 5.3.5.3.2 Table 1.22A and Lipsky *et al.*, 2000

Source: Applicant’s November 14, 2014 response to IR

BLA 125544  
CT-P13  
Celltrion, Inc.

In order to facilitate the review of your submission, provide the requested information no later than February 17, 2015. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/February 5, 2015  
Cleared by: GLevin/February 5, 2015  
RDavi/February 5, 2015  
LJafari/February 5, 2015  
TBBT/February 5, 2015  
Finalized by: NTon/February 5, 2015

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PHUONG N TON  
02/05/2015



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

---

**Date:** February 4, 2015

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648
<b>Subject:</b> BLA 125544 CT-P13 CMC Microbiology Information Request	

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**Comments:** Please acknowledge receipt and respond by 9 AM February 17, 2015

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Document to be emailed to: [Sally.Choe@parexel.com](mailto:Sally.Choe@parexel.com)

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Dear Dr. Choe:

We are reviewing your submission dated August 8, 2014, and have the following requests for information:

1. With regard to the bioburden testing of the [REDACTED] (b) (4) the bioburden data do not provide meaningful information because the sample is collected and tested immediately after [REDACTED] (b) (4). The bioburden and endotoxin samples should be representative of worst-case processing conditions for time and temperature. Move the bioburden and endotoxin sampling of the [REDACTED] (b) (4) to the end of the hold time.
2. With regard to the hold time validation of the [REDACTED] (b) (4)  
[REDACTED]
3. [REDACTED] (b) (4)  
[REDACTED]
4. In your amendment dated October 27, 2014, (Sequence 6) response to DP question 5, you indicate that the [REDACTED] (b) (4)  
[REDACTED]
5. Provide results of [REDACTED] (b) (4) and summary environmental monitoring data obtained during the media fills conducted on November 19, 2013, November 26, 2013, December 3, 2013, and November 7, 2014, [REDACTED] (b) (4).
6. Because the [REDACTED] (b) (4)  
[REDACTED]

7. You indicate in your amendment dated January 15, 2015, (Sequence 16) response to question 6(c) that the nominal bioburden sample volume for [REDACTED] (b) (4)
8. You indicate that the [REDACTED] (b) (4)
9. Only the [REDACTED] (b) (4)
10. With regard to the [REDACTED] (b) (4)
11. The [REDACTED] (b) (4)
12. With regard to [REDACTED] (b) (4)
13. Establish a [REDACTED] (b) (4)
14. Provide the locations of [REDACTED] (b) (4)  
[REDACTED] A diagram would be helpful.
15. Provide information and summary validation data for [REDACTED] (b) (4)
16. With regard to shipping validation, [REDACTED] (b) (4)

BLA 125544  
CT-P13  
Celltrion, Inc.

17. Provide information and summary data for the rabbit pyrogen test for CT-P13 drug product as required in 21 CFR 610.13(b).

In order to facilitate the review of your submission, provide the requested information no later than 9 AM, February 17, 2015. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/February 3, 2015  
Cleared by: CBo/February 3, 2015  
PHughes/February 3, 2015  
LJafari/February 3, 2015  
TBBT/February 3, 2015  
Finalized by: NTon/February 4, 2015

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PHUONG N TON  
02/04/2015



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Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** January 29, 2015

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 Statistics Information Request

Total no. of pages including  
cover and signature page 3

**Comments:** Please acknowledge receipt and respond by February 5, 2015

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Document to be emailed to: Sally.Choel@parexel.com

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BLA 125544  
CT-P13  
Celltrion, Inc.

Dear Dr. Choe:

We are reviewing your submission dated August 8, 2014, and have the following request for information:

Your protocols and study reports for Studies 1.1 and 3.1 indicate that “The study was unblinded at Week 30 for reporting; however, the study remained blinded to the investigators and patients until the end of the study.” Clarify what is meant by this statement. In particular, did investigators and patients remain blinded only to treatment assignment, or did they remain blinded to Week 30 results as well? If the latter, how was blinding maintained?

In order to facilitate the review of your submission, provide the requested information no later than February 5, 2015. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/January 28, 2015  
Cleared by: GLevin/January 28, 2015  
RDavi/January 28, 2015  
LJafari/January 28, 2015  
TBBT/January 29, 2015  
Finalized by: NTon/January 29, 2015

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/s/  
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PHUONG N TON  
01/29/2015



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

---

**Date:** January 14, 2015

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 Clinical Pharmacology Information Request

Total no. of pages including  
cover and signature page 3

**Comments:** Please acknowledge receipt and respond by January 22, 2015

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Document to be emailed to: Sally.Choe@parexel.com

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BLA 125544  
CT-P13  
Celltrion, Inc.

Dear Dr. Choe:

We are reviewing your submission dated August 8, 2014, and have the following requests for information:

Submit the following datasets to support the population pharmacokinetic analysis:

1. Provide all datasets used for model development. Submit validation as a SAS transport files (\*.xpt). Provide a description of each data item in a Define.pdf file. Flag and maintain any data point and/or subjects that have been excluded from the analysis in the datasets.
2. Provide Model codes or control streams. Provide output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submit these files as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).

In order to facilitate the review of your submission, provide the requested information no later than January 22, 2015. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/January 14, 2015  
Cleared by: LJafari/January 14, 2015  
SBrar/January 14, 2015  
LHe/January 14, 2015  
TBBT/January 14, 2015  
Finalized by: NTon/January 14, 2015

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/s/  
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PHUONG N TON  
01/14/2015



JAN 13 2015

HyunJu Yang  
Celltrion Inc.  
23, Academy-ro, Yeonsu-gu  
Incheon, 406-840  
Republic of Korea

**RE: Request for Refund of Fiscal Year 2015 Annual Biosimilar Biological Product Development Fee**

Dear Ms. Yang:

This letter is in response to your October 15, 2014, email from Jennifer Seiler requesting a refund of Celltrion's fiscal year (FY) 2015<sup>1</sup> annual Biological Product Development (BPD) fee, paid under the user fee provisions of the Federal Food, Drug, and Cosmetic Act (the Act)<sup>2</sup>, for IND 118135. For the reasons described below, the Food and Drug Administration (FDA or the Agency) denies the refund of the FY 2015 BPD fee; however, the Agency has issued Celltrion a partial refund of the FY 2014<sup>3</sup> application fee for, BLA 125544 for \$233,520.00.

The Biosimilar User Fee Act (BsUFA) prohibits refunds of any BPD fees<sup>4</sup>. Celltrion was required to pay the FY 2015 BPD fee by October 1, 2014, since its application was not going to be accepted for filing by the fee due date.<sup>5</sup> An annual BPD fee for a product is assessed unless a marketing application for that product is submitted and accepted for filing, or participation in the BPD program is discontinued.<sup>6</sup> Celltrion paid the FY 2014 application fee on July 16, 2014, and submitted the marketing application on August 8, 2014. Upon submission of the application, FDA commenced its 60-day filing review, which was expected to take the full 60 days and conclude after the FY 2015 BPD fee due date of October 1, 2014. The application was accepted for filing on October 7, 2014.

BsUFA requires the reduction of the *application fee* in the amount of all "cumulative" BPD fees paid, including fees paid shortly after an application is submitted for filing but before FDA files the application<sup>7</sup>. The statute does not limit the BPD fees in question to those paid as of the date

<sup>1</sup> FY 2015 = October 1, 2014 through September 30, 2015

<sup>2</sup> Sections 744G and 744H of the Act (21 U.S.C. §379j-51 and 379j-52).

<sup>3</sup> FY 2014 = October 1, 2013 through September 30, 2014

<sup>4</sup> 21 U.S.C. § 379j-52(a)(1)(F)

<sup>5</sup> The due date for annual BPD fees is the first business day on or after October 1 of each fiscal year, or the first business day after the enactment of an appropriations Act providing for the collection and obligation of fees for such fiscal year, whichever is later. See 21 U.S.C. § 379-j52(a)(1)(B)(ii).

<sup>6</sup> 21 U.S.C. § 379j-52(a)(1)(B)(iii).

<sup>7</sup> 21 U.S.C. § 379j-52(a)(2)(A)(i)

of the applications submission. Pursuant to 21 U.S.C. § 379j-52(g), Celltrion requested a refund within 180 days of the FY 2015 BPD fee due date. As a result, a partial refund of the application fee in the amount of \$233,520.00 was issued to Celltrion on November 7, 2014 (check number (b) (4)). Ms. Seiler confirmed on December 2, 2014, that Celltrion has received the check.

If you have any questions about this matter, please contact Beena Alex or Jacqueline LeeHoffman at 301-796-7900.

Sincerely,



Donal Parks, Director  
Division of User Fee Management and Budget Formulation  
Office of Management  
Center for Drug Evaluation and Research

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/s/  
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BEENA N ALEX  
01/13/2015

## MEMORANDUM

**To:** File for Celltrion, Inc.'s 351(k) Application, BLA # 125544, Referencing Remicade (infliximab)

**From:** The CDER Exclusivity Board

**Re:** Exclusivity Expiry for Remicade (infliximab) BLA 103772

**Date:** October 3, 2014

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The CDER Exclusivity Board (Board) was asked by the Therapeutic Biologics and Biosimilars Team (TBBT) in CDER's Office of New Drugs to determine if there is any unexpired exclusivity under section 351(k)(7) of the Public Health Service (PHS) Act for Remicade (infliximab) (BLA 103772; Janssen Biotech, Inc.) that would prohibit the submission, or approval, of any 351(k) application for a proposed biosimilar (or interchangeable) to Remicade (infliximab).

Section 351(k)(7)(A) of the PHS Act states that "approval of ... [a biosimilar application] may not be made effective by the Secretary until the date that is 12 years after the date on which the reference product was first licensed under subsection (a)." Section 351(k)(7)(B) of the PHS Act states that ... [a biosimilar application] may not be submitted to the Secretary until the date that is 4 years after the date on which the reference product was first licensed under subsection (a)." Section 351(k)(7)(C)(i) of the PHS Act states that "[s]ubparagraphs (A) and (B) shall not apply to a license for or approval of ... a supplement for the biological product that is the reference product."

After reviewing the record, the Board concludes that BLA 103772 for Remicade (infliximab) was first licensed by FDA under section 351(a) of the PHS Act on August 24, 1998. The product was initially indicated for the treatment of moderately to severely active Crohn's disease for the reduction of the signs and symptoms, in patients who have an inadequate response to conventional therapies; and treatment of patients with fistulizing Crohn's disease for the reduction in the number of draining enterocutaneous fistula(s). Between November 10, 1999 and September 23, 2011, numerous supplements were approved to expand this indication, and to add indications for pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis. Additional supplements for changes and updates to the approved labeling were approved since first licensure and up to November 6, 2013.

The dates that are 4 and 12 years after the date of first licensure of Remicade (infliximab) are August 24, 2002, and August 24, 2010, respectively. A licensure of a supplement does not trigger a separate period of exclusivity. Accordingly, section 351(k)(7) of the PHS Act does not prohibit the submission, or approval, of any 351(k) application for a proposed biosimilar (or interchangeable) to Remicade (infliximab).

**Cc:** The Therapeutics Biosimilar Biologics Team, Office of New Drugs, CDER  
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)/ODE II/CDER  
Sandra Benton, Marlene Schultz-DePalo

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/s/  
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MARLENE T SCHULTZ-DEPALO

12/30/2014

Memo entered into DARRTS on behalf of the CDER Exclusivity Board



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

---

**Date:** December 22, 2014

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 CMC Microbiology Information Request

Total no. of pages including  
cover and signature page 4

**Comments:** Please acknowledge receipt and respond by January 19, 2015

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Document to be emailed to: Sally.Choe@parexel.com

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Dear Dr. Choe:

We are reviewing your submission dated August 8, 2014, and have the following requests for information:

1. The endotoxin acceptance criteria of (b) (4) EU/mL for the (b) (4) exceed the drug product endotoxin specification of (b) (4) EU/mL. The contribution of endotoxin from (b) (4) could potentially cause the drug product to fail the endotoxin specification. Correct this inconsistency. If you increase the drug product endotoxin specification, the contribution of endotoxin from (b) (4) should be considered.
2. With regard to the (b) (4) process,
  - Justify why the validation runs did not use worse-case process parameters compare to the routine production runs.
  - Justify why the acceptance criteria for validation runs do not include minimum dwell time above a defined temperature.
  - Provide the methods and controls used to monitor routine production runs.
  - Briefly describe the requalification program for the (b) (4).
3. Provide information and summary validation data for the vial (b) (4)
4. With regard to the shipping validation studies of the CT-P13 drug product you committed to conduct, clarify if the studies were (will be) conducted during the worst-case temperature conditions (summer and winter). Because the (b) (4) varies depending on the ambient temperature the shippers are exposed to, the external temperature does have effect on how long the (b) (4) (b) (4) Provide the acceptance criteria for temperature and duration of the studies. Clarify when the summary shipping validation data will be provided. In addition, for routine drug product shipping, confirm that the temperature of the load during each shipment is monitored and documented.
5. Clarify which endotoxin method (b) (4) the DP endotoxin test at each site.
6. With regard to the (b) (4)
7. With regard to the endotoxin (b) (4)

(b) (4)



8. The labeling in the facility diagrams provided in Section 3.2.A.1, “Facilities and equipment” for the DP facility is not legible. Provide diagrams of better quality.

In order to facilitate the review of your submission, provide the requested information no later than January 19, 2015. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/December 22, 2014  
Cleared by: BChi/December 22, 2014  
PHughes/December 22, 2014  
LJafari/December 22, 2014  
TBBT/December 22, 2014  
Finalized by: NTon/December 22, 2014

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/s/  
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PHUONG N TON  
12/22/2014



**Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II**

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**ELECTRONIC CORRESPONDENCE**

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**Date:** December 16, 2014

<b>To:</b> Sally Choe, Ph.D. Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648
<b>Subject:</b> BLA 125544 CT-P13 CMC Microbiology Information Request	

Total no. of pages including  
cover and signature page 6

**Comments:** Please acknowledge receipt and respond by January 12, 2015

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Document to be emailed to: Sally.Choel@parexel.com

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Dear Dr. Choe:

We are reviewing your submission dated August 8, 2014, and have the following requests for information:

1. With regard to the container closure integrity (CCI) tests for drug product container closure,
  - Provide the sensitivity of the microbial ingress test and the correlation to that of the dye ingress and pressure decay tests as soon as the information is available.
  - Explain how the positive controls are prepared for the studies provided in Table 3.2.P.2.5-1. Provide the results of the positive and negative controls for the studies.
  - Describe how the vacuum pressure decay test is conducted and the challenges applied to the vials during the test.
2. We recommend conducting container closure integrity test in lieu of sterility test for stability samples annually and at expiry. Describe the container closure integrity test that will be used on the stability program, including the challenge conditions, sensitivity of the test (smallest breach size the test can detect), and how the positive controls will be prepared.
3. You indicate that the target capping head height is (b) (4). Provide the unit for head height.
4. Clarify if the (b) (4)
5. The hold time for (b) (4)
6. With regard to the (b) (4) processing,
  - (b) (4)

- The hold time in the [REDACTED] (b) (4)

- Monitor product bioburden and endotoxin at the [REDACTED] (b) (4)

7. The provided [REDACTED] (b) (4)

8. With regard to the DP [REDACTED] (b) (4)

9. Describe the environmental monitoring program during media fill runs and routine production runs.

10. With regard to [REDACTED] (b) (4)

[REDACTED] (b) (4)

[Redacted] (b) (4)

11. Your response in amendment dated October 1, 2014 (Sequence 4) question 4 indicates that

[Redacted] (b) (4)

12. Provide validation data and information for [Redacted] (b) (4)

[Redacted]

13. Provide the bioburden, endotoxin, particle, [Redacted] (b) (4)

[Redacted]

14. The acceptance criteria for [Redacted] (b) (4)

[Redacted]

15. Clarify why temperature and hold time are not included in the acceptance criteria [Redacted] (b) (4)

[Redacted]

16. With regard to [Redacted] (b) (4)

[Redacted]

17. Provide the protocols and reports for the [Redacted] (b) (4)

[Redacted]

BLA 125544  
CT-P13  
Celltrion, Inc.

(b) (4)

In order to facilitate the review of your submission, provide the requested information no later than January 12, 2015. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/December 15, 2014  
Cleared by: BChi/December 15, 2014  
PHughes/December 15, 2014  
LJafari/December 15, 2014  
TBBT/December 16, 2014  
Finalized by: NTon/December 16, 2014

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/s/  
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PHUONG N TON  
12/16/2014



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** December 10, 2014

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Ste 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 Microbial Quality-Drug Substance  
Information Request

Total no. of pages including  
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**Comments:** Please acknowledge receipt and respond by December 23, 2014

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Document to be emailed to: [Sally.Choe@parexel.com](mailto:Sally.Choe@parexel.com)

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Dear Dr. Choe:

We are reviewing your BLA dated August 8, 2014, and your submission dated October 27, 2014, which was in response to our information request correspondence dated September 26, 2014. We have the following additional requests for information:

**Description of the Manufacturing Process and Process Controls – Batches and Scale  
Definition – Upstream Manufacturing Process and Process Controls**

With regard to your response to question 1.d, bioburden test volume of (b) (4) is too low and may not have enough sensitivity. Test volume should be (b) (4).

**Description of the Manufacturing Process and Process Controls – Batches and Scale  
Definition – Downstream Manufacturing Process and Process Controls**

With regard to your response to question 2.f, bioburden sample (b) (4)

(b) (4)

With regard to your response to question 2.k, provide endotoxin limits for product (b) (4)

(b) (4)

**Process Validation and/or Evaluation – Validation Batches**

With regard to your response to question 4, indicate if load bioburden samples for (b) (4)

(b) (4)

**Process Validation and/or Evaluation – In-Process Hold Validation**

With regard to your response to question 5.b, indicate if the product (b) (4)

(b) (4)

**Control of Drug Substance – Specifications**

With regard to your response to question 7.b, although the (b) (4)

(b) (4)

(b) (4)

**Control of Drug Substance – Analytical Procedures**

With regard to your response to question 8, for th

(b) (4)

**Control of Drug Substance – Validation of Analytical Procedures (Bioburden)**

With regard to your response to question 9.e, clarify if sample  
bulk drug substance for batches 09PCM0308, E12200B03, E12200B04, and E12200B05 are  
identical to those used for the commercial process.

(b) (4)

**Control of Drug Substance – Validation of Analytical Procedures (Endotoxin)**

With regard to your response to question 10.d, clarify the purpose and conclusion of the  
endotoxin stability study in report P2-MVER-30215. Indicate if endotoxin was spiked before or  
after storage of samples. If the samples were

(b) (4)

In order to facilitate the review of your submission, provide the requested information no later than the close of business December 23, 2014. You may submit your response via telephone facsimile at 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/December 9, 2014  
Cleared by: RCandauchacon/December 9, 2014  
PHughes/December 9, 2014  
LJafari/December 9, 2014  
TBBT/December 9, 2014  
Finalized by: NTon/December 10, 2014

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/s/  
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PHUONG N TON  
12/10/2014



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**Date:** December 10, 2014

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Ste 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 Clinical Information Request

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Total no. of pages including  
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**Comments:** Please acknowledge receipt and respond by December 19, 2014

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Document to be emailed to: [Sally.Choe@parexel.com](mailto:Sally.Choe@parexel.com)

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Dear Dr. Choe:

We are reviewing your BLA dated August 8, 2014, and we have the following additional requests for information:

1. We note discrepancies between tables 14.1.1, 14.3.1.6, and 12-9 from CSR 3.1. Explain the discrepancies for the following:
  - a. Table 14.1.1 indicates a significant imbalance in the life-threatening infusion-related anaphylactic reaction leading to discontinuation, i.e. 6 (2%) patients in CT-P13 group vs. none in the Remicade group.

CELLTRION, Inc.  
 Protocol: CT-P13 3.1

Confidential  
 Page 1 of 3

Table 14.1.1  
 Patient Disposition  
 All-Randomized Population

	CT-P13 3 mg/kg (N=302)	Remicade 3 mg/kg (N=304)	Total (N=606)
<b>Total Number of Patients</b>			
Screened [1]			1077
Randomized	302 (100.0%)	304 (100.0%)	606 (100.0%)
Initiated Treatment	300 (99.3%)	302 (99.3%)	602 (99.3%)
<b>Completed</b>	233 (77.2%)	222 (73.0%)	455 (75.1%)
<b>Discontinued</b>	69 (22.8%)	82 (27.0%)	151 (24.9%)
<b>Primary Reason for Discontinuation</b>			
Lack of efficacy	10 (3.3%)	6 (2.0%)	16 (2.6%)
Adverse event	31 (10.3%)	41 (13.5%)	72 (11.9%)
Life-threatening infusion-related anaphylactic reaction	6 (2.0%)	0	6 (1.0%)
Diabetes mellitus	0	0	0
Other adverse event	25 (8.3%)	41 (13.5%)	66 (10.9%)

Note: The all-randomized population will be used as the denominator for percentages.

[1] This includes screening failures and randomized patients. If a patient is screened and randomized, the treatment assignment will be displayed in the 'Randomized' row.

[2] Only for patients who prematurely discontinue study drug.

[3] This summary includes screening failures and non-randomized patients only.

Source Data: Listings 16.2.1.1 and 16.2.2.3

\Celltrion CLTP1331RA\Week 54 DBL Run\TLF\T140101.SAS Executed: 31AUG2012 07:45

- b. In contrast, Table 14.3.1.6 lists a different number of patients with permanent discontinuation in the categories of Infusion related reaction, Anaphylactic reaction, and Anaphylactic shock.

Table 14.3.1.6  
 Treatment-emergent Adverse Events leading to permanent discontinuation of study drug  
 Safety population

	CT-P13 3 mg/kg (N=302)	Remicade 3 mg/kg (N=300)	Total (N=602)
<b>Infusion related reaction</b>	<b>5 ( 1.7%)</b>	<b>8 ( 2.7%)</b>	<b>13 ( 2.2%)</b>
Related	5 ( 1.7%)	8 ( 2.7%)	13 ( 2.2%)
Mild	1 ( 0.3%)	1 ( 0.3%)	2 ( 0.3%)
Moderate	2 ( 0.7%)	6 ( 2.0%)	8 ( 1.3%)
Severe	2 ( 0.7%)	1 ( 0.3%)	3 ( 0.5%)
Immune system disorders	7 ( 2.3%)	6 ( 2.0%)	13 ( 2.2%)
Related	7 ( 2.3%)	6 ( 2.0%)	13 ( 2.2%)
Mild	2 ( 0.7%)	1 ( 0.3%)	3 ( 0.5%)
Moderate	2 ( 0.7%)	5 ( 1.7%)	7 ( 1.2%)
Severe	3 ( 1.0%)	0	3 ( 0.5%)
<b>Anaphylactic reaction</b>	<b>3 ( 1.0%)</b>	<b>1 ( 0.3%)</b>	<b>4 ( 0.7%)</b>
Related	3 ( 1.0%)	1 ( 0.3%)	4 ( 0.7%)
Moderate	1 ( 0.3%)	1 ( 0.3%)	2 ( 0.3%)
Severe	2 ( 0.7%)	0	2 ( 0.3%)

Note: The total number of TEAEs count includes all patient events which lead to permanent study drug discontinuation. At each level of summarization, a patient is counted once if they reported one or more events leading to study drug discontinuation. Only the most severe event is counted. The event is considered to be related if the relationship is defined as 'possible', 'probable' or 'definite'.  
 [1] From the MedDRA dictionary, version 13.1.

Source Data: Listing 14.3.2.4  
 \Celltrion CLTP1331RA\Week 54 CSR\TLF\T14030106.SAS Executed: 18DEC2012 06:04

Table 14.3.1.6  
 Treatment-emergent Adverse Events leading to permanent discontinuation of study drug  
 Safety population

	CT-P13 3 mg/kg (N=302)	Remicade 3 mg/kg (N=300)	Total (N=602)
<b>Anaphylactic shock</b>	<b>1 ( 0.3%)</b>	<b>0</b>	<b>1 ( 0.2%)</b>
Related	1 ( 0.3%)	0	1 ( 0.2%)
Severe	1 ( 0.3%)	0	1 ( 0.2%)
Drug hypersensitivity	3 ( 1.0%)	5 ( 1.7%)	8 ( 1.3%)
Related	3 ( 1.0%)	5 ( 1.7%)	8 ( 1.3%)
Mild	2 ( 0.7%)	1 ( 0.3%)	3 ( 0.5%)
Moderate	1 ( 0.3%)	4 ( 1.3%)	5 ( 0.8%)

- c. Further, Table 12-9 (Treatment-Emergent Serious Adverse Events Possibly due to Drug Hypersensitivity or Infusion-Related Reactions: Safety Population) lists 4 patients in the CT-P13 group with anaphylactic shock/reaction, and 2 patients with infusion-related reactions. In the Remicade group, 3 patients had infusion related reactions resulting in permanent discontinuation.

**Table 12-9 Treatment-Emergent Serious Adverse Events Possibly Due to Drug Hypersensitivity or Infusion-Related Reactions: Safety Population**

System Organ Class Preferred Term	Treatment Group	Patient Number	Adverse Event	Serious Criteria	Action Taken	Medical Monitor Comment
<b>General disorders and administration site conditions</b>						
Infusion-related reaction	CT-P13	2308-3003	Infusion-related reaction	Important medical event	Permanently discontinued	-
Infusion-related reaction	CT-P13	1807-3008	Infusion reaction	Hospitalization, initial, life threatening	Permanently discontinued	-
Infusion-related reaction	Remicade	0308-3015	Infusion-related reaction	Important medical event	Permanently discontinued	-
Infusion-related reaction	Remicade	1807-3001	Infusion reaction (bronchospasm, dyspnoea, palpitation, abdominal pain)	Hospitalization, initial	Permanently discontinued	-
Infusion-related reaction	Remicade	1808-3008	Infusion reaction	Important medical event	Permanently discontinued	-
<b>Immune system disorders</b>						
Anaphylactic reaction	CT-P13	0601-3010	Infusion-related reaction "anaphylaxis"	Life threatening	Permanently discontinued	No hospitalization required
Anaphylactic shock	CT-P13	1801-3006	Anaphylactic shock	Life threatening	Permanently discontinued	No hospitalization required
Anaphylactic reaction	CT-P13	1807-3011	Anaphylaxis	Life-threatening, important medical event	Permanently discontinued	Hospitalization for administrative reasons only
Drug hypersensitivity	Remicade	1808-3013	Study drug reaction (hyperaemia of face and neck, dyspnoea)	Important medical event	Permanently discontinued	-

Page 176

System Organ Class Preferred Term	Treatment Group	Patient Number	Adverse Event	Serious Criteria	Action Taken	Medical Monitor Comment
Anaphylactic reaction	CT-P13	1406-3006	Infusion-related anaphylactic reaction	Important medical event	Permanently discontinued	

Note: The treatment-emergent serious adverse events included in this table are those considered by the medical monitor to be possibly related to drug hypersensitivity or infusion-related reaction.

Source: [Data Listings 14.3.2.3 and 16.2.7.1 \(Appendix 16.2.7\)](#).

2. Provide definitions and severity grading used to capture and report the following adverse events of special interest:

- Infusion-related reactions
- Anaphylactic reaction
- Hypersensitivity reactions
- Immune system disorder
- General disorders and administration site conditions

3. In the Summary of Clinical Safety, Section 2.7.4.2.7.3.3.2 Anaphylactic Reactions According to Criteria by Sampson *et al.*, (2006) you indicate that the criteria published by Sampson *et al.*, (2006) were used to scrutinize the safety database of the CT-P13 clinical program for serious and severe infusion-related reaction cases meeting these criteria. However, since

BLA 125544  
CT-P13  
Celltrion, Inc.

these criteria are designed to prospectively capture potential cases of anaphylaxis, provide details on the methodology used to retrospectively query your database.

In order to facilitate the review of your submission, provide the requested information no later than the close of business Friday, December 19, 2014. You may submit your response via telephone facsimile at 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/December 10, 2014  
Cleared by: LJafari/December 10, 2014  
              TBBT/December 10, 2014  
              JWaheed/December 10, 2014  
              NNikolov/December 10, 2014  
Finalized by: NTon/December 10, 2014

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/s/  
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PHUONG N TON  
12/10/2014

## Harris, Sarah

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**From:** Harris, Sarah  
**Sent:** Tuesday, November 25, 2014 3:54 PM  
**To:** 'Seiler, Jennifer'  
**Cc:** Ton, Phuong Nina; Choe, Sally  
**Subject:** RE: BLA125544 [REDACTED] (b) (4)

**Follow Up Flag:** Follow up  
**Flag Status:** Flagged

**Categories:** DPARP

Hi Jennifer,

Thank you for your inquiry. Please proceed with your submission. We have no further comments at this time.

Kind Regards,  
Sarah

---

**From:** Seiler, Jennifer [<mailto:Jennifer.Seiler@parexel.com>]  
**Sent:** Tuesday, November 25, 2014 11:41 AM  
**To:** Harris, Sarah  
**Cc:** Ton, Phuong Nina; Choe, Sally  
**Subject:** BLA125544 [REDACTED] (b) (4)

Hi Sarah,

The sponsor for BLA 125544 has a question regarding their plan to submit [REDACTED] (b) (4) for their product under review. The sponsor is submitting the request for review of the [REDACTED] (b) (4) this week (as advised in the Type IV meeting minutes, the sponsor was asked to request review of [REDACTED] (b) (4) [REDACTED] (b) (4)). In this [REDACTED] (b) (4) review request, the sponsor is providing explanation that the [REDACTED] (b) (4). Do you have a sense that this approach would be acceptable for [REDACTED] (b) (4)? Please let us know if you think anything additional would be needed for your review.

Kind regards,  
Jennifer

**Jennifer A. Seiler, PhD, RAC**  
Senior Consultant

**PAREXEL International**  
4600 East-West Highway  
Suite 350  
Bethesda, MD, USA, 20814  
T +1 301.634.8034  
F +1 301.634.8040  
M [REDACTED] (b) (6)  
[Jennifer.Seiler@PAREXEL.com](mailto:Jennifer.Seiler@PAREXEL.com)  
[www.PAREXEL.com](http://www.PAREXEL.com)



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/s/  
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SARAH J HARRIS  
11/26/2014



Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

---

**Date:** November 20, 2014

<b>To:</b> Sally Choe, PhD Senior Director, Parexel International	<b>From:</b> Nina Ton, Pharm.D. Regulatory Project Manager
<b>Applicant:</b> Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b> 301-634-8040	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 301-634-8010	<b>Phone number:</b> 301-796-1648

**Subject:** BLA 125544 CT-P13 Information Request

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Total no. of pages including  
cover and signature page: 3

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**Comments:** Please acknowledge receipt and respond by November 28, 2014

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Document to be emailed to: Sally.Choe@parexel.com

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BLA 125544  
CT-P13  
Celltrion, Inc.

Dear Dr. Choe:

We are reviewing your 351(k) BLA dated August 8, 2014, and your submission dated November 14, 2014. We have the following request for information:

We have been unable to exactly replicate your primary analysis results for Study 3.1. Explain why one subject (subjid #22093010) was classified as an ACR20 responder at Week 30 despite a protocol-prohibited change in medication (according to the variable “crit6fl” in the ADaM dataset ADACR). Clarify, for a particular row of the ADACR dataset, whether the non-responder flag variables “crit6fl” and “crit7fl” indicate that a subject had a protocol-prohibited medication change and surgical joint procedure respectively prior to the time of the ACR assessment represented by that row of the dataset, or if those variables are flagging medication changes and joint procedures occurring at any time through Week 54. If the latter, indicate where the date of the medication change or joint procedure can be located, or submit a new ADACR dataset containing new variables serving as flags for medication changes and joint procedures that occurred *prior to the time of the ACR assessment*.

In order to facilitate the review of your submission, provide the requested information no later than the close of business Friday, November 28, 2014. You may submit your response via telephone facsimile at 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13  
Celltrion, Inc.

Drafted by: NTon/November 18, 2014  
Cleared by: GLevin/November 18 and 20, 2014  
LJafari/November 18, 2014  
TBBT/November 20, 2014  
Finalized by: NTon/November 20, 2014

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/s/  
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PHUONG N TON  
11/20/2014

## Harris, Sarah

---

**From:** Harris, Sarah  
**Sent:** Friday, November 14, 2014 9:56 AM  
**To:** 'Seiler, Jennifer'  
**Cc:** Choe, Sally; Ton, Phuong Nina  
**Subject:** BLA 125544- Response to Proprietary Name Inquiry

**Follow Up Flag:** Follow up  
**Flag Status:** Flagged

**Categories:** DPARP

Hi Jennifer,

In reference to your Biologics License Application (BLA 125544) for CT-P13 and your November 12, 2014 email inquiry regarding a Request for Proprietary Name Review, please see our response below:

Parexel Question on behalf of Celltrion:

[REDACTED] (b) (4)  
?"

FDA Response:

[REDACTED] (b) (4)  
The associated goal dates will be 3  
months for reviewing the proposed name (b) (4)  
Although you can expect to receive a determination on the acceptability of a (b) (4)  
name within 90 days, [REDACTED] (b) (4)

Kind regards,  
Sarah

Sarah Harris, PharmD  
Safety Regulatory Project Manager | OSE | CDER | FDA  
[sarah.harris@fda.hhs.gov](mailto:sarah.harris@fda.hhs.gov) | 240.402.4774

Sarah Harris, PharmD  
Safety Regulatory Project Manager | OSE | CDER | FDA  
[sarah.harris@fda.hhs.gov](mailto:sarah.harris@fda.hhs.gov) | 240.402.4774

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/s/  
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SARAH J HARRIS  
11/14/2014



**Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II**

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**ELECTRONIC TRANSMITTAL SHEET**

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Date: November 5, 2014

To: Sally Choe, PhD Senior Director, Parexel International	From: Nina Ton, Pharm.D. Regulatory Project Manager
Sponsor: Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 301-634-8040	Fax number: 301-796-9728
Phone number: 301-634-8010	Phone number: 301-796-1648

Subject: BLA 125544 CT-P13 Information Request

Total no. of pages including  
cover and signature page: 3

Comments: Please acknowledge receipt and respond by November 13, 2014

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Document to be emailed to: Sally.Choe@parexel.com

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BLA 125544  
CT-P13 (a proposed biosimilar to Remicade)  
Celltrion, Inc.

Dear Dr. Choe:

We are reviewing your BLA dated August 8, 2014, and have the following requests for information:

The patient data listings requested for Clinical Study Sites #2007 (Pedro Miranda, MD), #1215 (Pawel Hrycaj, MD), #1213 (Slamowir Jeka, MD), and #1214 (Janusz Jaworski, MD), respectively appear incomplete.

For the above applicable clinical study sites, submit complete primary study endpoint patient data listing raw individual scores to include the following ACR20 (CT-P13 3.1) study endpoint individual raw scores or values from baseline to end of study:

- Assessment of the 68 tender joints
- Assessment of the 66 joints
- Patient assessment of pain (VAS scale, in millimeters)
- Patient global assessment of disease activity (VAS scale, in millimeters)
- Physician global assessment of disease activity (VAS scale, in millimeters)
- Health Assessment Questionnaire (HAQ) estimate of physical ability
- Inflammatory marker laboratory results: Serum C-Reactive Protein (CRP, mg/dL) concentration or Erythrocyte Sedimentation Rate (ESR, mm/h)

Also, please include the following ASAS20 and ASAS40 (Study CT-P13 1.1) individual raw scores for the above applicable studies:

- Patient global assessment of disease status (Appendix 6.8)
- Patient assessment of spinal pain (Appendix 6.9)
- Function according to BASFI (Appendix 6.6)
- Morning stiffness determined using the last 2 questions of BASDAI

In order to facilitate the review of your submission, provide the requested information no later than the close of business Thursday, November 13, 2014. You may submit your response via telephone facsimile at 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544  
CT-P13 (a proposed biosimilar to Remicade)  
Celltrion, Inc.

Drafted by: NTon/November 4, 2014  
Cleared by: SNabavian/November 4, 2014  
              AOrencia/November 4, 2014  
              TBBT/November 5, 2014  
Finalized by: NTon/November 5, 2014

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/s/  
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PHUONG N TON  
11/05/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

IND 118135  
BLA 125544/0

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

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

ATTENTION: Sally Choe, PhD  
Senior Director

Dear Dr. Choe:

Please refer to:

- your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CT-P13, 10 mg/mL; and
- your Biologics License Application (BLA) dated and received August 8, 2014, submitted under section 351(k) of the Public Health Service Act for CT-P13, 10 mg/mL.

We also refer to:

- your correspondence, dated and received May 20, 2014, requesting review of your proposed proprietary name, (b) (4) for your IND; and
- your correspondence dated and received September 26, 2014, requesting review of your proposed proprietary name, (b) (4) for your 351(k) BLA.

We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your September 26, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sarah Harris, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4774. For any other information regarding this application, contact Nina Ton, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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KELLIE A TAYLOR  
10/28/2014

**From:** Alex, Beena  
**To:** [Lund, Ileana](#)  
**Cc:** [Parks, Donal](#); [Lee, Jacqueline](#)  
**Subject:** Refund Request by Celltrion  
**Date:** Thursday, October 16, 2014 11:19:00 AM  
**Attachments:** [RE Refund Request.msg](#)

---

Hi Ileana,

The request is for a partial refund of the application fee in the amount of \$233,520 since the FY15 annual BPD fee was not reduced from the application fee.

Please see the attached email for the address and DUNS number. Additional information is below.

BLA: 125544

Receipt Date: July 16, 2014

User Fee ID: 4000056

Amount paid: \$1,756,310

Amount to refund: \$233,520

Please let me know if you need additional information.

Thanks,  
Beena

Beena Alex, MPH, MBA  
Division of User Fee Management & Budget Formulation  
Office of Management | Center for Drug Evaluation and Research  
W051, Room 6281  
Phone: 240.402.4797 | Email: [Beena.Alex@fda.hhs.gov](mailto:Beena.Alex@fda.hhs.gov)

**From:** [Seiler, Jennifer](#)  
**To:** [Alex, Beena](#)  
**Subject:** RE: Refund Request  
**Date:** Thursday, October 16, 2014 9:59:41 AM

---

Hi Beena,

Thank you for the explanation, I understand the refund will come from the BLA application fee. Let me know if you need anything else.

Regards,  
Jennifer

**Jennifer A. Seiler, PhD, RAC**  
Senior Consultant  
[PAREXEL International](#)  
T +1 301.634.8034  
F +1 301.634.8040  
M (b) (6)

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---

**From:** Alex, Beena [<mailto:Beena.Alex@fda.hhs.gov>]  
**Sent:** Thursday, October 16, 2014 9:26 AM  
**To:** Seiler, Jennifer  
**Subject:** RE: Refund Request

Good morning Jennifer,

We cannot refund any initial or annual biosimilar biological product development (BPD) fees in accordance with Section 744H(a)(1)(F)(i) of the Federal Food, Drug and Cosmetic Act. As a result, a refund cannot be processed for the payment received on September 26, 2014 for the FY15 annual BPD fee for IND 118135. However, we do consider the application fee that was received on July 16, 2014 for BLA 125544 as an overpayment since the FY15 annual BPD fee was not reduced from the application fee as per Section 744H(a)(2)(A)(i) of the Act. Therefore, we can grant a partial refund of the application fee in the amount of \$233,520.00. Please let me know if you have any other questions.

Regards,  
Beena

**Beena Alex, MPH, MBA**  
Office of Management | Center for Drug Evaluation and Research

Food and Drug Administration  
10903 New Hampshire Ave  
Silver Spring, MD 20993  
Phone: 240.402.4797 | Email: [Beena.Alex@fda.hhs.gov](mailto:Beena.Alex@fda.hhs.gov)

---

**From:** Seiler, Jennifer [<mailto:Jennifer.Seiler@parexel.com>]  
**Sent:** Wednesday, October 15, 2014 4:22 PM  
**To:** Alex, Beena  
**Subject:** RE: Refund Request

Hi Beena,

This is a formal request for a refund from the Agency concerning recent biologic product fee payments. Please see below for details:

Name of applicant requesting the refund, including company name, address, point of contact, telephone and facsimile numbers, and email address:

- **Celltrion Inc.**  
23, Academy-ro, Yeonsu-gu,  
Incheon, 406-840,  
Republic of Korea
- **Contact Name:** HyunJu.Yang ([HyunJu.Yang@celltrion.com](mailto:HyunJu.Yang@celltrion.com))
- **Tel:** +82-32-850-5000
- **Fax:** +82-32-850-6593

IND #/BLA #

- IND 118135
- BLA 125544

Identification of the specific fee(s) for which the refund is requested

- A refund is being requested for the FY2015 Annual BPD fee for IND 118135 in the amount of \$233,520 made on Sept 26, 2014 (payment reference number (b) (4))

Reason for the refund request

- BLA 125544 was submitted to the Agency on Aug 8, 2014. The BLA application fee did not subtract the FY2015 annual BPD fee as the invoice for that amount had not yet been received by Celltrion. We were advised by FDA to pay the FY2015 Annual fee so as not to incur a financial hold on the IND or BLA applications. Celltrion considers the additional payment on Sept 26, 2014 an overpayment, and would like to request a refund.

Date on which payment was made or will be made of the fee for which a refund is requested

- The fee we are requesting a refund for was made on Sept 26, 2014.

Where the refund request should be mailed to:

- See above address and contact information.

Tax ID number (required for all domestic companies) or DUNS number (required for all foreign companies)

- DUNS number: (b) (4)

If it is possible to provide us with confirmation when the refund has been issued, or tracking number if sent via courier, that would be helpful (if you are provided with this information). If there is anything you need, please let me know.

Kind regards,  
Jennifer

**Jennifer A. Seiler, PhD, RAC**

Senior Consultant

PAREXEL International

T +1 301.634.8034

F +1 301.634.8040

M (b) (6)

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**From:** Alex, Beena [<mailto:Beena.Alex@fda.hhs.gov>]

**Sent:** Wednesday, October 15, 2014 10:56 AM

**To:** Seiler, Jennifer

**Subject:** Refund Request

Dear Jennifer,

Please submit a formal request for a refund and include the following information:

- Name of applicant requesting the refund, including company name, address, point of contact, telephone and facsimile numbers, and email address
- IND #/BLA #
- Identification of the specific fee(s) for which the refund is requested
- Reason for the refund request
- Date on which payment was made or will be made of the fee for which a refund is requested
- Where the refund request should be mailed to
- Tax ID number (required for all domestic companies) or DUNS number (required for all foreign companies)

Please let me know if you have any questions. I can be reached at 240-402-4797.

Thanks,  
Beena

**Beena Alex, MPH, MBA**

Office of Management | Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Ave  
Silver Spring, MD 20993  
Phone: 240.402.4797 | Email: [Beena.Alex@fda.hhs.gov](mailto:Beena.Alex@fda.hhs.gov)

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/s/  
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BEENA N ALEX  
10/21/2014



BLA 125544

**FILING COMMUNICATION –  
NO FILING REVIEW ISSUES IDENTIFIED**

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

Attention: Sally Choe, PhD  
Senior Director, Parexel International

Dear Dr. Choe:

Please refer to your Biologics License Application (BLA) dated August 8, 2014, received August 8, 2014, submitted under section 351(k) of the Public Health Service Act for CT-P13.

CT-P13 is a proposed biosimilar to US-licensed Remicade (infliximab) (BLA 103772).

We also refer to your amendments dated September 5, 22, and 26, and October 1 and 20, 2014.

We refer to the October 7, 2014, filing notification letter informing you that your 351(k) BLA has been accepted for review with a standard review classification and a June 8, 2015, user fee goal date.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by May 11, 2015.

We are currently planning to hold an advisory committee meeting to discuss this application. The tentative dates for the meeting are March 26 or 27, 2015.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information by November 12, 2014:

1. In the primary analysis of ACR20 in Study 3.1, it appears that patients who discontinued the study, initiated a protocol-prohibited medication change, underwent a surgical joint procedure during the study, or had missing data on a component of ACR20 were considered non-responders. Therefore, the primary outcome is in fact a composite measure; however the proportion of patients who meet each non-response criterion should be described. Submit tables of results at key time points in Study 3.1 that break down the non-responder subgroups according to the following mutually exclusive reasons: (1) remained in the study with complete ACR component assessments at the time point of interest, and did not meet the ACR20 response criteria; (2) withdrew from the study prior to the time point of interest (with further breakdown according to primary reason for withdrawal); (3) did not meet criterion (1) or (2), and had a protocol-prohibited change in medication prior to the time point of interest; (4) did not meet the previous criteria and required a surgical joint procedure prior to the time point of interest; and (5) did not meet the previous criteria and had missing data on an ACR20 component(s) at the time point of interest. An example table shell is provided below. In addition, please provide the code used for the analysis and clarify all of the data sources.

	<b>CT-P13</b>	<b>EU-approved Remicade (infliximab)</b>	<b>Overall</b>
Responder			
Non-responder			
Did not meet ACR response criteria			
Discontinued study			
Lack of Efficacy			
Adverse Event			
Withdrawal of Consent			
Other			
Prohibited Medication Change			
Surgical Joint Procedure			
Missing/Incomplete ACR assessment			

2. For key safety and efficacy endpoints, submit and discuss results from subgroup analyses by sex, race, and age. Also include tests for the treatment-by-subgroup interactions.
3. Provide more details on the re-evaluation of radiographic data, including when, why, and how the re-evaluation took place. Also, submit the code and identify the data sources that were used for the re-evaluation, or indicate where this information can be found in the submission.
4. Provide all notes (including closed session minutes) from meetings of the Data Safety Monitoring Board during Study 3.1.

## **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following issues related to the format of labeling and have the following labeling comments:

1. A horizontal line must separate Highlights (HL) from the Table of Contents (TOC) and another horizontal line must separate the TOC from the Full Prescribing Information (FPI).
2. Extend the horizontal line with the heading **INDICATIONS AND USAGE** over the entire width of the column.
3. Add white space before each major heading in HL and delete the white space after each major heading in HL.
4. The revision date is not right justified. Move the second page of HL to the right column of the page.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by November 12, 2014. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions.

## **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list

each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, the proposed package insert (PI), and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

We acknowledge receipt of your requests for waivers and a deferral of pediatric studies for this application. Once we have reviewed your requests, we may follow up with additional comments.

If you have any questions, call Nina Ton, Regulatory Project Manager, at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, MD, PhD  
Director  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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BADRUL A CHOWDHURY  
10/21/2014



**Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II**

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**ELECTRONIC TRANSMITTAL SHEET**

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Date: October 16, 2014

To: Sally Choe, Ph.D. Senior Director, Parexel International	From: Nina Ton, Pharm.D. Regulatory Project Manager
Company: Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 301-634-8040	Fax number: 301-796-9728
Phone number: 301-634-8010	Phone number: 301-796-1648

Subject: BLA 125544 CT-P13 Information Request

Total no. of pages including cover and signature page 3

Comments: Please acknowledge receipt and respond by October 22, 2014

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Document to be emailed to: Sally.Choe@parexel.com

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Dear Dr. Choe:

We are reviewing your BLA dated August 8, 2014, and have the following requests for information:

1. Submit all the subject data listings grouped under each clinical study site, for each individual study protocol in PDF electronic format for Protocol CT-P13 3.1 (rheumatoid arthritis) and Protocol CT-P13 1.1 (ankylosing spondylitis), respectively, for the Chile Site 2007 (Pedro Miranda, MD), and the study sites in Poland (Site 1215, Pawel Hrycaj, MD; Site 1213, Slawomir Jeka, MD; and Site 1214, Januz Jaworski, MD).

The study subject data listings should capture the following, as applicable:

- a. Subject discontinuation (If applicable per treatment group: site subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation)
  - b. All adverse events (If applicable per treatment group: preferred term/investigator entry, date start/stopped, severity/resolution, Serious Adverse Event (yes, no), death (yes/no))
  - c. Primary efficacy endpoint/s site subject number, visit # and corresponding date (baseline, week 1...end-of-study visit or Week 54, etc)
  - d. Protocol deviations or violations
2. Provide an updated contact information listing of the principal study investigators for your clinical study sites for Protocol CT-P13 3.1 (rheumatoid arthritis) and Protocol CT-P13 1.1 (ankylosing spondylitis). Specifically, for each study site PI, provide an updated phone number and email address.
  3. Indicate where your clinical trial data is located. If the data is still with a CRO or another sponsor sub-company or affiliate outside the U.S., provide the contact information including physical street address, phone number, email address, and the responsible person.

In order to facilitate the review of your submission, provide the requested information no later than the close of business Wednesday, October 22, 2014. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544

Drafted by: NTon/October 15, 2014  
Cleared by: SBarnes/October 15, 2014  
NNikolov/October 15, 2014  
AOrencia (DSI)/October 16, 2014  
Finalized by: NTon/October 16, 2014

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/s/  
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PHUONG N TON  
10/16/2014



BLA 125544

**FILING NOTIFICATION LETTER**

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

Attention: Sally Choe, PhD  
Senior Director, Parexel International

Dear Dr. Choe:

Please refer to your Biologics License Application (BLA) dated August 8, 2014, received August 8, 2014, submitted under section 351(k) of the Public Health Service Act for CT-P13.

CT-P13 is a proposed biosimilar to Remicade (infliximab) (BLA 103772).

We also refer to your amendments dated September 5, 22, and 26, and October 1, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. This filing communication constitutes the notification described in section 351(l)(2) of the Public Health Service Act that your 351(k) BLA has been accepted for review. The review classification for this application is **Standard**. Therefore, the user fee goal date is June 8, 2015.

We plan to send a separate filing communication that provides additional information and describes any potential review issues identified during the initial filing review within 74 calendar days from the date of FDA receipt of the original submission in accordance with the performance goal established under the Biosimilar User Fee Act (BsUFA).

If you have any questions, call Nina Ton, Regulatory Project Manager, at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, MD, PhD  
Director  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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BADRUL A CHOWDHURY  
10/07/2014



**Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II**

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**ELECTRONIC TRANSMITTAL SHEET**

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Date: October 1, 2014

To: Sally Choe, Ph.D. Senior Director, Parexel International	From: Nina Ton, Pharm.D. Regulatory Project Manager
Company: Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 301-634-8040	Fax number: 301-796-9728
Phone number: 301-634-8010	Phone number: 301-796-1648

Subject: BLA 125544 CT-P13 Information Request

Total no. of pages including  
cover and signature page      3

Comments: Please acknowledge receipt and respond by the close of  
business Friday, October 3, 2014

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Document to be emailed to: Sally.Choel@parexel.com

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copying, or other action based on the content of this communication is not  
authorized. If you have received this document in error, please notify us  
immediately by telephone at (301) 796-2300. Thank you.**

BLA 125544

Dear Dr. Choe:

We are reviewing your submission dated August 8, 2014, and have the following request for information:

1. Submit the coding dictionary used for mapping investigator verbatim terms to preferred terms. If submitting as a PDF document, include mapping in both directions (verbatim -> preferred and preferred -> verbatim).

In order to facilitate the review of your submission, provide the requested information no later than the close of business Friday, October 3, 2014. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544

Drafted by: NTon/October 1, 2014  
Cleared by: LJafari/October 1, 2014  
              JWaheed/October 1, 2014  
              NNikolov/October 1, 2014  
Finalized by: NTon/October 1, 2014

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/s/  
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PHUONG N TON  
10/01/2014



**Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II**

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**ELECTRONIC TRANSMITTAL SHEET**

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Date: September 26, 2014

To: Sally Choe, Ph.D. Senior Director, Parexel International	From: Nina Ton, Pharm.D. Regulatory Project Manager
Company: Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 301-634-8040	Fax number: 301-796-9728
Phone number: 301-634-8010	Phone number: 301-796-1648

Subject: BLA 125544 CT-P13 Microbial Quality Information Request

Total no. of pages including  
cover and signature page      8

Comments: Please acknowledge receipt and respond by October 24, 2014

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Document to be emailed to: [Sally.Choe@parexel.com](mailto:Sally.Choe@parexel.com)

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Dear Dr. Choe:

We are reviewing your submission dated August 8, 2014, and have the following requests for information:

**The following requests pertain to the drug substance section**

1. Description of the Manufacturing Process and Process Controls – Batches and Scale Definition – Upstream Manufacturing Process and Process Controls



2. Description of the Manufacturing Process and Process Controls – Batches and Scale Definition – Downstream Manufacturing Process and Process Controls

Provide the following information:





(b) (4)

3. Control of Critical Steps and Intermediates



(b) (4)

4. Process Validation and/or Evaluation – Validation Batches

Section 3.2.S.2.4.4.11 and Table 3.2.S.2.4-26 shows a bioburden in-process sample during



(b) (4)

5. Process Validation and/or Evaluation – In-Process Hold Validation

- a. Clarify if the hold time study described in section 3.2.S.2.5.9.1 of the submission was conducted in the manufacturing



(b) (4)

- b. Submit summary protocol and results for the (b) (4) conducted (b) (4)
- c. Indicate if the maximum hold time established (b) (4)

6. Process Validation and/or Evaluation – Shipping Validation

- a. Indicate if temperature loggers are routinely used during drug substance shipping and submit a diagram with their placement.
- b. Indicate if acceptance criteria are established for the temperature and duration of the shipping from (b) (4).

7. Control of Drug Substance – Specifications

- a. Describe how endotoxin and bioburden release samples are taken.
- b. Drug substance stored under (b) (4)
- c. Drug substance endotoxin release specifications (b) (4)

8. Control of Drug Substance – Analytical Procedures

Describe in detail the bioburden and endotoxin analytical methods for (b) (4) samples and DS release

9. Control of Drug Substance – Validation of Analytical Procedures (Bioburden)

Submit bioburden test method qualification protocol and qualification report. Include the following information:

- a. Preparation of negative controls, inoculum control and positive controls.
- b. Preparation of test samples, (b) (4)
- c. Media and incubation conditions for each organism and comparison with standard routine testing.

- d. Specify what is considered “ (b) (4) ”.
- e. Indicate which bioburden results correspond to each of the DS batches used for the bioburden test method qualification and the origin of batches 09PCM0308, E12200B03, E12200B04, and E12200B05 (they are not consistent with the batch number system submitted in section 3.2.S.2.2.1 of the BLA).
- f. Indicate if the bioburden test method has been qualified for all in-process samples and provide method qualification description, acceptance criteria, and results.
- g. Indicate if the bioburden test will be conducted in (b) (4) facilities and if there is any difference in the way that the method is conducted in either facility

10. Control of Drug Substance – Validation of Analytical Procedures (Endotoxin)

Submit endotoxin test method qualification protocol and qualification report. Include the following information:

- a. Describe the preparation of test samples, positive and negative controls, number of replicates per sample, nominal endotoxin spike and endotoxin values recovered in (b) (4).
- b. Provide criteria for the standard curve, including number of replicates, endotoxin concentration, and acceptance criteria for the coefficient of regression.
- c. Provide drug substance (b) (4).
- d. Indicate if the endotoxin method has been qualified for (b) (4).
- e. Recent studies suggest that the (b) (4).

**The following requests pertain to the drug product section**

1. Provide summary validation data of the container closure integrity tests used to determine the integrity of the CT-P13 drug product primary container closure. Include the sensitivity of the tests [REDACTED] (b) (4) [REDACTED] and dye solution concentration and microbial challenge concentration. The sensitivity of the microbial ingress test should be correlated to that of the dye ingress test.
2. Provide summary container closure integrity test results form CP-P13 vials crimped using the worst-case crimping parameters [REDACTED] (b) (4). Explain how the positive controls for the routine container closure integrity tests are prepared.
3. Provide the protocol and validation reports for the [REDACTED] (b) (4) [REDACTED]. Include endotoxin reduction and lethality data. In addition, provide a comparison of the process parameters used during routine production and validation studies.
4. Provide the protocol and reports for [REDACTED] (b) (4) CT-P13 product-contact equipment from three runs.
5. Provide the protocol and reports for [REDACTED] (b) (4) [REDACTED]
6. Provide protocol and reports for three most recent consecutive media fill runs validating the filling process of the CT-P13 drug product. [REDACTED] (b) (4) [REDACTED]
7. The drug product formulation contains [REDACTED] (b) (4) [REDACTED]

(b) (4)

In order to facilitate the review of your submission, provide the requested information by October 24, 2014. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544

Drafted by: NTon/September 25, 2014  
Cleared by: RCandauchacon/September 25 and 26, 2014  
BChi/September 25, 2014  
PHughes/September 25, 2014  
LJafari/September 26, 2014  
TBBT/September 26, 2014  
Finalized by: NTon/September 26, 2014

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/s/  
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PHUONG N TON  
09/26/2014



**Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II**

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**ELECTRONIC TRANSMITTAL SHEET**

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Date: September 23, 2014

To: Sally Choe, Ph.D. Senior Director, Parexel International	From: Nina Ton, Pharm.D. Regulatory Project Manager
Company: Celltrion, Inc. c/o Parexel International 4600 East-West Highway, Suite 350 Bethesda, MD 20814	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: 301-634-8040	Fax number: 301-796-9728
Phone number: 301-634-8010	Phone number: 301-796-1648

Subject: BLA 125544 CT-P13 Information Request

Total no. of pages including cover and signature page 3

Comments: Please acknowledge receipt and respond by the close of business Friday, September 26, 2014

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Document to be emailed to: Sally.Choel@parexel.com

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Dear Dr. Choe:

We are reviewing your submission dated August 8, 2014, and have the following requests for information:

1. Provide the microbial retention validation study report for the [REDACTED] <sup>(b) (4)</sup> for CT-P13 drug product.
2. Provide information and summary data for the rabbit pyrogen test for CT-P13 drug product as required in 21CFR610.13(b). The rabbit pyrogen test should be performed with three product lots to demonstrate that your product does not contain pyrogenic substances other than bacterial endotoxin.
3. Provide the summary validation data and information for the sterilization validation of the lyophilizer(s) from three runs.
4. Clarify if the [REDACTED] <sup>(b) (4)</sup> process at Celltrion.

In order to facilitate the review of your submission, provide the requested information no later than the close of business Friday, September 26, 2014. You may submit your response by fax to 301-796-9728, or by email to [phuong.ton@fda.hhs.gov](mailto:phuong.ton@fda.hhs.gov), followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125544

Drafted by: NTon/September 23, 2014  
Cleared by: BChi/September 23, 2014  
PHughes/September 23, 2014  
LJafari/September 23, 2014  
Finalized by: NTon/September 23, 2014

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/s/  
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PHUONG N TON  
09/23/2014



BLA 125544

**BLA ACKNOWLEDGEMENT**

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

Attention: Sally Choe, Ph.D.  
Senior Director, Parexel International

Dear Dr. Choe:

We have received your Biologics License Application (BLA) submitted under section 351(k) of the Public Health Service Act (PHS Act) for the following:

**Name of Biological Product:** CT-P13, a proposed biosimilar to Remicade (infliximab)

**Date of Application:** August 8, 2014

**Date of Receipt:** August 8, 2014

**BLA Number:** 125544

**Proposed Indications:** Crohn's Disease (CD), Pediatric Crohn's Disease, Ulcerative Colitis (UC), Pediatric Ulcerative Colitis, Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), and Plaque Psoriasis (Ps)

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Pulmonary, Allergy, and Rheumatology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

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If you have any questions, call me at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Nina Ton, Pharm.D.  
Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PHUONG N TON  
08/20/2014



IND 118135

**MEETING MINUTES**

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

Attention: Sally Choe, Ph.D.  
Director, Parexel International

Dear Dr. Choe:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CT-P13.

We also refer to the meeting between representatives of your firm and the FDA on April 28, 2014. The purpose of the meeting was to discuss the format and content of a proposed Biologics License Application (BLA) to be submitted under section 351(k) of the Public Health Service Act for CT-P13, a proposed biosimilar to US-licensed Remicade (infliximab).

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

If you have any questions, call me at (301) 796-1648.

Sincerely,

*{See appended electronic signature page}*

Nina Ton, Pharm.D.  
Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



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

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Biosimilar  
**Meeting Category:** BPD Type 4

**Meeting Date and Time:** April 28, 2014; 2:00 – 3:30 PM EST  
**Meeting Location:** White Oak Building 22, Conference Room 1419

**Application Number:** IND 118135  
**Product Name:** CT-P13, a proposed biosimilar to US-licensed Remicade (infliximab)  
**Indication:** Sponsor is seeking the same indications for which US-licensed Remicade is approved  
**Sponsor Name:** Celltrion, Inc.

**Meeting Chair:** Badrul A. Chowdhury, M.D., Ph.D.  
**Meeting Recorder:** Nina Ton, Pharm.D

**FDA ATTENDEES**

Richard Moscicki, M.D., Deputy Center Director for Science Operations, Center for Drug Evaluation and Research (CDER)  
Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)  
Lydia Gilbert-McClain, M.D., Deputy Director, DPARP  
Sarah Yim, M.D., Supervisory Associate Director, DPARP  
Nikolay Nikolov, M.D., Clinical Team Leader, DPARP  
Juwaria Waheed, M.D., Clinical Reviewer, DPARP  
Marcie Wood, Ph.D., Pharmacology/Toxicology Team Leader, DPARP  
Matthew Whittaker, Ph.D., Pharmacology/Toxicology Reviewer, DPARP  
Ruthanna Davi, Ph.D., Biostatistics Reviewer, Division of Biometrics II, Office of Biostatistics (OB)  
Gregory Levin, Ph.D., Biostatistics Reviewer, Division of Biometrics II, OB  
Satjit Brar, Ph.D., Pharm.D., B.S., Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)  
Ping Ji, Ph.D., Clinical Pharmacology Reviewer, DCPII, OCP  
David Frucht, M.D., Chief, Laboratory of Cell Biology, Division of Monoclonal Antibodies (DMA), Office of Biotechnology Products (OBP)  
Kurt Brorson, Ph.D., Product Quality Reviewer, DMA, OBP  
Erik Read, Ph.D., Product Quality Reviewer, DMA, OBP  
Leah Christl, Ph.D., Associate Director for Therapeutic Biologics, Therapeutic Biologics and

Biosimilars Team (TBBT)  
Sue Lim, M.D., Senior Staff Fellow, TBBT  
Carla Lankford, M.D., Ph.D., Science Policy Analyst, TBBT  
Neel Patel, Pharm.D., Regulatory Project Manager, TBBT  
Tyree Newman, Sr. Regulatory Health Project Manager, TBBT  
Janice Weiner, J.D., M.P.H., Senior Regulatory Counsel, Division of Regulatory Policy I (DRP I), Office of Regulatory Policy (ORP)  
Daniel Orr, J.D., M.A., Regulatory Counsel, DRP I, ORP  
Teresa McMillan, Pharm.D., Safety Evaluator, Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology  
Robert Pratt, Pharm.D., Risk Management Analysts, Division of Risk Management, Office of Surveillance and Epidemiology  
David Kettl, M.D., Clinical Team Leader, Division of Dermatology and Dental Products  
Robert Fiorentino, M.D. Clinical Team Leader, Division of Gastroenterology and Inborn Errors Products  
Nina Ton, Pharm.D., Regulatory Project Manager, DPARP

## **SPONSOR ATTENDEES**

### **Celltrion Inc.**

SooYoung Lee, Ph.D., Director  
ByoungOh Kwon, MSc, Assistant Sr. Manager  
MinKyoung Jeon, Ph.D., Manager  
EunJu Jun, BSc, Assistant Manager  
Alex Kudrin, Ph.D., M.D., Vice President  
SungYoung Lee, MSc, Assistant Sr. Manager  
JiHye Yun, MSc, Assistant Sr. Manager  
SunHee Lee, MSc, Assistant Manager  
CheHwee Park, MSc, Assistant Sr. Manager  
HyeYoung Park, BSc, Assistant Manager  
Yumi Kim, BSc, Staff  
EunJin Bang, MSc, Staff  
Elizabeth Pollitt, Ph.D., Vice President  
SangJoon Lee, Ph.D., Vice President

### **Parexel Consulting**

Ravi Harapanhalli, Ph.D., Vice President

(b) (6)



## **1. BACKGROUND**

Celltrion submitted a BPD Type 4 Meeting Request dated February 6, 2014, to the Division of Pulmonary, Allergy, and Rheumatology Products, to discuss the format and content of a proposed Biologics License Application (BLA) to be submitted under section 351(k) of the Public Health Service Act (PHS Act) for CT-P13, a proposed biosimilar product to US-licensed Remicade (infliximab). The Division granted the meeting on February 18, 2014. FDA provided preliminary comments to Celltrion on April 25, 2014. After the review of these comments, Lotte McNamara, Parexel Senior Consultant, communicated to the Division via email dated April 27, 2014, that Celltrion requested to focus the meeting discussion to CMC Questions 1, 6, 8, 9, 12, 13, and Clinical Questions 15A, 22, and 24. Celltrion also had two additional questions which are included in the meeting minutes. In addition, Celltrion provided comments which are incorporated to the corresponding questions and also attached in Section 9. Celltrion's questions and comments are in *italics*, FDA's responses are in normal font, and the meeting discussion is in **bold**.

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

## **2. DISCUSSION**

### **CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)**

#### **Question 1**

*Does the Agency agree that the proposed bioassay is adequate for controlling drug substance and drug product bioactivity in support of the CT-P13 BLA submission and that a bioassay to control Fc-mediated functionality is not needed?*

#### **FDA Response**

The proposed cell-based bioassay appears appropriate for the intended purpose of assessing target-binding activity. However, the detailed procedure and adequacy of the validation will be a review issue.

An assay is still needed to ensure that Fc-mediated functions such as ADCC remain in control. While acceptance criteria for afucosylated glycoforms level could be an appropriate strategy to control changes in effector function such as ADCC, there may be other biochemical aspects by which ADCC and other effector activities could be affected which are not reflected by assessing and controlling afucosylation only.

A validated assay evaluating Fc function, including ADCC or FcγRIIIa binding with quantitative specifications for release testing is expected to be provided in the BLA submission.

**Celltrion’s Comment**

A validated assay evaluating the Fc effector function, FcγRIIIa binding with proposed quantitative specifications of (b) (4) % will be included in the drug substance specifications. However, considering that there is a clear correlation between afucosylation levels and FcγRIIIa binding as seen in Figure 1, (b) (4)

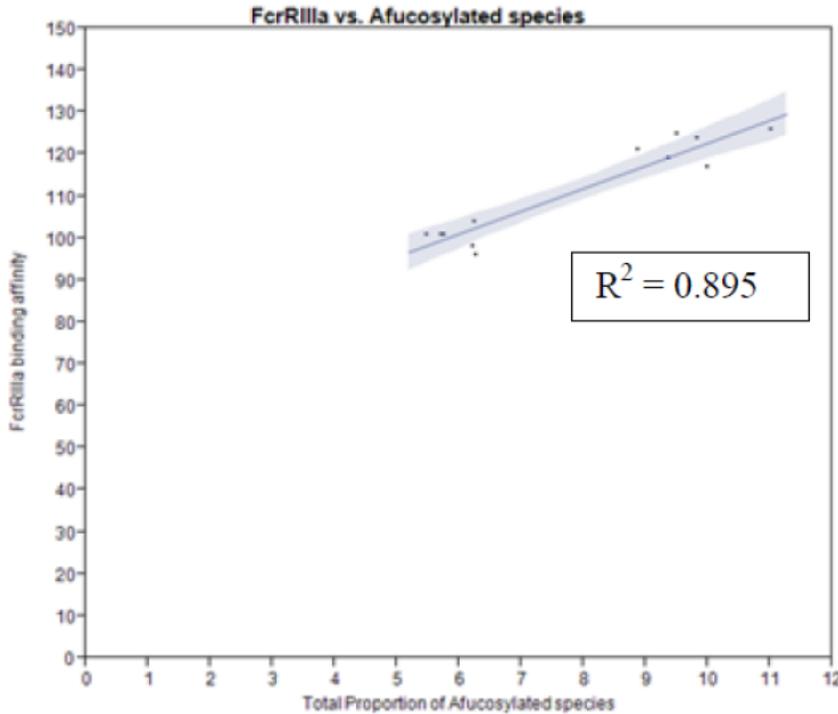


Figure 1: A Scatter Plot Showing Percent Afucosylated Glycan Species and FcγRIIIa Binding (n=12; 6 each CT-P13 and EU-approved Remicade®)

Data derived from IND amendment submitted on 06 February, 2014:  
Table 3.2.R-135: Summary of Afucosylation, FcγRIIIa Binding Affinity, ADCC (w/normal PBMC and NK cells) and CDC in CT-P13 and EU-approved Remicade® Batches.

Figure 3.2.R-62: A Scatter Plot Showing Percent Afucosylated Glycan Species and FcγRIIIa Binding

**Meeting Discussion**

As summarized in Celltrion’s comment above, Celltrion proposed to evaluate Fc effector function with a validated assay and release testing of (b) (4) drug substance lots. FDA confirmed that the proposed assay is the preferred assay as it measures biologic activity. The acceptability of Celltrion’s proposal (b) (4) would be a review issue and considered at such time as a supplement to the proposed 351(k) BLA may be submitted.

**Question 2**

Does the Agency agree that the proposed shelf-life and stability testing program are adequate to support the BLA submission of the CT-P13 Drug Product?

**FDA Response**

The proposed expiry-dating and stability testing program plans appear adequate for assessment of drug product manufactured at the current facilities. Assessment of drug product expiry-dating and stability will be a review issue.

**Meeting Discussion**

**This question was not discussed.**

**Question 3**

*The CT-P13 drug substance manufacturing process has been validated.*

*Does the FDA agree that the validation studies provide verification that the process is robust and consistently produces CT-P13 with the desired quality attributes meeting specifications?*

**FDA Response**

The necessary high-level elements of drug substance manufacturing process validation appear to be present. The adequacy of the validation exercise will be determined by a review of the data submitted in the BLA and upon inspection.

**Meeting Discussion**

**This question was not discussed.**

**Question 4**

*The CT-P13 drug product manufacturing has been validated.*

*Does the FDA agree that the validation studies provide verification that the process is robust and consistently produces CT-P13 with the desired quality attributes meeting specifications?*

**FDA Response**

The necessary high-level elements of drug product manufacturing process validation appear to be present. The adequacy of the validation exercise will be determined by a review of the data submitted in the BLA and upon inspection.

**Meeting Discussion**

**This question was not discussed.**

**Question 5**

*Stability assessment of CT-P13 has shown that the product remains within the proposed specifications through six months of accelerated stability testing and three months of high temperature stress testing, and one month at  $-25\pm 5^{\circ}\text{C}$ . The detailed stability data will be included in the BLA.*

*Does FDA concur with CELLTRION's view that additional temperature cycling study to support temperature excursions during shipping and transit may not be needed?*

**FDA Response**

Provide data supporting the conclusion that potential temperature excursions during shipping will remain within the range tested in the stability studies (b) (4). Otherwise, conduct stability studies of drug product lots exposed to the historical upper limit of exposure with respect to temperature for the duration of the entire shipping process. The acceptability of particular shipping validation studies will be a review and inspectional issue.

**Meeting Discussion**

**This question was not discussed.**

**Question 6**

*Regarding shipping validation studies to support the BLA, CELLTRION proposes to summarize in the BLA two earlier shipping studies conducted to transport drug substance (b) (4).*

*These studies represent worst case scenario with regard to time and temperature excursions and mechanical shock during transportation. Additionally, the BLA will include a shipping validation protocol supporting air transportation (b) (4).*

*The US-specific validation data will be submitted in an amendment to the BLA during the review process.*

*Does the FDA agree with the proposed approach to address shipping validation to support the BLA submission and review?*

**FDA Response**

The proposed approach appears appropriate if Celltrion commits to providing the temperature profile during shipping validation studies. However, final assessment of particular shipping validation studies will be a review and inspectional issue.

**Celltrion's Comment**

*The Sponsor proposes to include (b) (4) representative of the worst case configuration to accommodate various shipping configurations to different regions of the World.*

*(b) (4)*  
*This is considered worst case shipping conditions.*

*Does the FDA agree with the proposed shipping configuration for the shipping validation studies?*

**Meeting Discussion**

**Celltrion proposed to provide shipping validation studies for vials in carton containers only and not in an entire case. FDA concurred with this approach, but noted that the final assessment will be a review and inspectional issue. FDA expressed concerns over the range of temperature conditions that the product could experience during shipping under worst-case scenarios and the impact of temperature on product stability. Celltrion clarified that**

**they will address these concerns and will provide temperature monitoring data in the BLA submission.**

### **Post-meeting Addendum**

**Additional comments regarding shipping validation may be sent as separate correspondence.**

### **Question 7**

*CELLTRION has taken a standard approach to developing a control strategy for the manufacture of CT-P13 drug substance and drug product as follows: 1) Established a Quality Target Product Profile (QTPP) for CT-P13, 2) Identified Critical Quality Attributes (CQAs) of CT-P13, 3) Investigated quality attributes of the CT-P13 drug substance and formulation ingredients, 4) Established Critical Process Parameters (CPP), 5) Outlined pertinent control strategies to ensure CT-P13 consistently meets its QTPP. The CPPs were initially selected prior to undertaking process characterization studies during the course of the development of the CT-P13 commercial manufacturing process. Although, some CPPs were determined not have direct correlation to the CQAs during the course of process characterization, a conservative approach was taken and the process parameter initially identified as critical were maintained as such when establishing the CT-P13 control strategy. The control strategy will be summarized in this document and described in detail in the BLA.*

*Does the FDA concur with CELLTRION's control strategy for the manufacture of CT-P13 drug substance and drug product?*

### **FDA Response**

The proposed high-level approach for the control strategy appears appropriate. Assessment of the details and implementation of the control strategy and identified CPPs will be a review and inspectional issue.

### **Meeting Discussion**

**This question was not discussed.**

### **Question 8**

*As discussed during the BPD Type 3 meeting held on 10 July 2013, the following categories of new data have been generated in the enhanced 3-way quality similarity assessment and are summarized in this Briefing Document:*

- *Physicochemical analysis*
- *A full complement of Fc receptor and antigen binding assays (i.e., the SPR analytical methods used in the 2-way similarity study) were conducted including FcγRIIIa binding*
- *The NK cell ADCC assay results are included*
- *The LPS-stimulated monocytes ADCC assay*
- *Main mechanism of action study, including apoptosis, and reverse signaling*

*Does the FDA concur that all recommended studies have been conducted in an effort to demonstrate similarity of CT-P13 with US-licensed Remicade® and EU-approved Remicade®?*

*Based on the quality data provided, does the FDA concur that the 2-way analytical similarity assessment has adequately demonstrated similarity of CT-P13 to EU-approved Remicade® and that with the bridge established by the 3-way similarity assessment of the analytical data with US-licensed Remicade®, CT-P13 qualifies for a biosimilar program versus US-licensed Remicade® under Section 351(k) of the PHS Act?*

**FDA Response**

We acknowledge the enhanced 3-way analytical similarity program intended to provide more robust and complete analytical similarity data directly comparing CT-P13 with the reference product, US-licensed Remicade, and assess the analytical differences identified and discussed during the July 10, 2013 BPD Type 3 meeting. We note that differences between CT-P13 and US-licensed Remicade with respect to binding to FcγRIIIa, the relative percentage of afucosylated glycans, and ADCC activity remain. The adequacy of the data, including any justifications, and final acceptability of the assays and their validation, will be a review and/or inspectional issue, based upon the totality of the data submitted in the BLA.

We cannot make a determination as to whether analytical similarity has been adequately demonstrated between CT-P13, US-licensed Remicade, and EU-approved infliximab (the latter for purposes of evaluating the relevance of comparative data with EU-approved infliximab to an assessment of biosimilarity to US-licensed Remicade) without review of the full data package, which should include primary data (e.g., sensograms, gel images, chromatograms, etc.) and not only summary data.

**Celltrion's Comment**

*We agree to include primary data from the similarity studies. We propose to include primary data from [REDACTED] <sup>(b)(4)</sup> of CT-P13, US-licensed Remicade® and EU-approved Remicade®. All other primary data will be available on-site during inspection. Does the FDA agree with this plan?*

*We have conducted an extensive battery of qualification studies for all the characterization methods. We intend to provide method description and qualification summary tables for assays used for characterization of similarity. For methods used for similarity assessments which are also used for release testing, a cross-reference will be provided to 3.2.S.4.3 and 3.2.P.5.3, as appropriate. The full qualification reports are available upon request and/or during inspection. Does the FDA concur with this approach?*

*We would like to inform the FDA that it is not feasible to fully qualify certain characterization assays whilst qualification has been completed for the assays considered most critical.*

**Dose-response curve confirmed, but additional qualification was not feasible:**

- *ADCC using whole blood (inherent variability in whole blood from different donors)*
- *Macrophage induction (inherent variability)*
- *Suppression of T-cell proliferation (inherent variability)*

**Assay qualification was not feasible:**

- *ADCC using LPS-stimulated monocytes as target cells and PBMC as effector cells (no response from LPS-stimulated monocytes; appropriate positive and negative controls were included in the studies)*
- *Wound healing (inherent variability, qualitative assay, negative control: no wound healing was observed from non-regulatory macrophages)*

### **Meeting Discussion**

Celltrion proposed to submit the primary data from (b) (4) of the drug products (CT-P13, US-licensed Remicade, and EU-approved infliximab) and the remainder of the data would be available during inspection. The Sponsor justified this approach by stating that submitting primary data on (b) (4) for the submission.

Celltrion also added that extensive qualification data, including method validation for assays used for the similarity assessment, would be provided along with cross references for those methods that are also used for release testing. All of these data would be provided in the BLA submission.

FDA indicated that since Celltrion's proposal was received just prior to the meeting, FDA would need further discussion on Celltrion's proposal and would provide a response as a post-meeting addendum.

Celltrion outlined in their comments that it would not be feasible to fully qualify certain characterization assays. FDA advised Celltrion to provide the available data and justify why a given assay could not be fully qualified. FDA also advised that if fully qualified characterization assays existed that measured the same attribute as an assay that could not be fully qualified, Celltrion should identify the orthogonal method(s) as part of the justification and provide the corresponding data. Celltrion agreed to provide all qualification data and submit justification for the assays that could not be fully qualified.

### **Post-meeting Addendum**

We do not agree with your proposal to submit the primary data from (b) (4) of CT-P13, US-licensed Remicade and EU-approved infliximab in the BLA, with the remaining primary data available on-site during inspection. Review of the primary data is a BLA review issue, and not an inspectional issue.

We acknowledge Celltrion's statement during the meeting that submission of the primary data (b) (4); however, you should submit a sufficient amount of primary data to substantiate your summary data from all tested lots and support your demonstration that your proposed product is highly similar to US-licensed Remicade. We recommend that Celltrion submit primary analytical similarity data (e.g. photographic quality graphic images of chromatograms, sensograms, electrophoretograms, overlaid plots of dilution series from bioassays) from a minimum of three lots (each) of CT-P13, US-licensed Remicade, and EU-approved infliximab in the original BLA. The chosen lots should span the available production or expiry dating range for each product. This information should also be provided in a tabular format. FDA will provide more detailed

**advice in a separate correspondence regarding the submission and type of primary data to support a determination of analytical similarity for your proposed 351(k) BLA. The primary data from the other 21 lots must be available upon request during the review cycle.**

**In addition to the primary data from a minimum of 3 lots each of CT-P13, US-licensed Remicade, and EU-approved infliximab, Celltrion should provide the results of the release and characterization assays for all lots included in the similarity exercise. These data should be provided in a tabular format grouped by product group (i.e., CT-P13 vs. US-licensed Remicade vs. EU-approved infliximab), along with the average, standard deviation, median, range, and 95% confidence interval determined from the assay data for each product group.**

**Regarding the amount of qualification data for characterization and release methods, Celltrion should submit all available data in the original BLA, regardless of whether the assay was fully qualified.**

#### **Question 9**

*As discussed during the BPD Type 3 meeting held on 10 July 2013, enhanced 3-way similarity assessment data covering 7 additional batches of each product (CT-P13, US-licensed Remicade® and EU-approved Remicade®) has been provided including statistical analysis of variance.*

*Does the FDA concur that together with the abridged 3-way similarity assessment data (which included 3 batches of each product) an adequate number of batches of each product have been tested to provide sufficient statistical power for the similarity assessment?*

#### **FDA Response**

As discussed during the July 10, 2013 BPD Type 3 meeting in relation to Question 12, the number of lots tested and the statistical analysis should be adequately justified by Celltrion. The adequacy of the analytical similarity assessment will be a review issue.

#### **Celltrion's Comment**

*Based on the outcome of the discussions during the BPD Type 3 meeting, the Sponsor has included analysis of an additional 7 batches of each product (CT-P13, US-licensed Remicade® and EU-approved Remicade®) including statistical analysis of variance. The data is provided in Table 22 and 23 (pages 113 and 114) of the Briefing Document.*

*Does the FDA agree with the statistical approach taken to evaluate the data (Bartlett's test and Welch's test for data showing significant difference in the Bartlett's test) or can you recommend an alternate statistical evaluation approach that may be more appropriate?*

*Does the FDA agree that if there is sufficient statistical power in the current analysis the number of batches selected for similarity assessment are adequate?*

#### **Meeting Discussion**

**Celltrion stated that data from 7 additional lots of each product were added to the similarity assessment and asked FDA if their proposed statistical approach was acceptable.**

**Regarding the number of lots tested in the analytical similarity assessment, Celltrion acknowledged that the number of lots would depend on lot-to-lot variability but asked FDA how many lots would be needed to provide sufficient statistical power for the similarity assessment. FDA noted that they did not have comments at this time on the statistical approach being proposed by Celltrion, but would endeavor to provide any comments as a post-meeting addendum. FDA clarified that, based on the intent of the analysis, Celltrion should consider power as the probability of the statistical approach ruling out a certain magnitude difference, and noted that a lack of evidence to demonstrate a difference was not evidence of no difference.**

**Post-meeting Addendum**

**FDA will provide comments on Celltrion's proposal as a separate correspondence.**

**Question 10**

*Residual risk due to the presence of higher amounts of H2L1 in CT-P13 relative to that observed in US-licensed and EU-approved Remicade® is addressed in the abridged as well as enhanced 3-way similarity assessment by showing that H2L1 fragment is a product-related substance (not an impurity) based on soluble TNF $\alpha$  binding and neutralization assays.*

*Does the FDA concur with CELLTRION's position that based on the CMC and clinical data provided in this briefing document comparing CT-P13 versus US-licensed and EU-approved Remicade®, residual risk to CT-P13 safety and efficacy is adequately addressed?*

**FDA Response**

We agree that residual risk from the presence of higher amounts of H2L1 on the safety and efficacy profile of CT-P13 appears to have been adequately addressed.

**Meeting Discussion**

**This question was not discussed.**

**Question 11**

*As requested during the BPD Type 3 meeting held on 10 July 2013, the NK enrichment procedure is described and these cells are shown to be sensitive to Fc $\gamma$ RIIIa binding changes. Complete description of the procedures for both the PBMC and NK ADCC assays, including their qualification is provided.*

*Does the FDA concur that the provided data and information is adequate for submission to the BLA?*

**FDA Response**

The assay descriptions and procedures provided in the package appear sufficiently detailed for review in the planned BLA submission. The adequacy of the data generated by the assays, and the qualification of the assays will be a review and inspectional issue.

**Meeting Discussion**

**This question was not discussed.**

### **Question 12**

*To address the residual risk due to the observed difference of near 23% in the FcγRIIIa binding, many different ADCC assays were undertaken with different effector and target cells during the enhanced 3-way assessment. Most importantly, when the most representative in vitro model for mimicking the in vivo environment (using LPS-stimulated monocytes as target cells), no ADCC activity was seen with CT-P13 or Reference Product (RP) or EU-approved Remicade®. Similar results were observed in the 2-way similarity assessment between CT-P13 and EU-approved Remicade® described in the IND 118135. Also, full complement of ADCC were repeated using RP to reaffirm the premise that ADCC is not considered a mechanism of action, which is also consistent with the data from public literature.*

*Does the FDA concur with CELLTRION that residual risk due to the differences in the ADCC assay results has been adequately addressed in the data generated from the abridged and enhanced 3-way similarity assessments?*

### **FDA Response**

Whether the observed 23% difference in FcγRIIIa binding between EU-approved infliximab and CT-P13 was adequately addressed with the additional assessments will be a review issue based upon the totality of the data submitted for review in the BLA. In addition, as discussed during the July 10, 2013 BPD Type 3 meeting in relation to Questions 11 and 12, Celltrion should provide a robust analytical similarity assessment between CT-P13 and US-licensed Remicade, including an adequate analysis of any observed differences. The results of such an assessment will also be a review issue based upon the totality of the data submitted.

### **Celltrion's Comment**

*Following our BPD Type 3 meeting in July 2013, we have submitted additional data to support the abridged 3-way as well as the enhanced 3-way assessments. Please refer to Question 8 for the additional data provided.*

*In addition, the clinical data related to the MoA and extrapolation also discusses the effect of observed differences in FcγRIIIa binding on clinical efficacy and safety.*

*Does the FDA agree that the data provided from the enhanced 3-way similarity assessment facilitates the evaluation of the totality of evidence related to the absence of impact of FcγRIIIa binding on safety and efficacy?*

### **Meeting Discussion**

**Celltrion noted that additional data had been submitted to the IND following the July 2013 meeting with FDA to address the observed differences in FcγRIIIa binding and asked if FDA had additional recommendations.**

**FDA commented that Celltrion had analyzed 10 lots each of US-licensed Remicade and CT-P13, and that the adequacy of the assays used and number of lots would be a review issue. FDA noted that Celltrion had included assays that focused on assessing the mechanism(s) of action of the products in RA. However, Celltrion should address any other mechanism(s) of action of the products in the other conditions of use for which Celltrion is seeking licensure, as Celltrion is proposing to extrapolate to other conditions of use for which US-licensed Remicade was licensed. However, FDA noted that they were not**

**necessarily recommending additional testing at this time, and reiterated that the acceptability of the data and any associated justification would be a review issue.**

### **Question 13**

*Considering that the primary mechanism of action as well as critical Fc functionality were addressed using RP in the abridged 3-way assessment as well as tested further in the enhanced 3-way assessment, additional secondary studies (induction of regulatory macrophages, inhibition of T-cell proliferation and promotion of wound healing) using RP are considered unnecessary as they are not expected to be different from those already conducted using EU-approved Remicade®.*

*Does FDA concur?*

### **FDA Response**

Section 351(k)(2)(A)(i)(II) of the PHS Act requires that a 351(k) application for a proposed biosimilar product include information demonstrating that the proposed biosimilar product and the reference product utilize the same mechanism or mechanisms of action for the condition(s) of use for which licensure is sought, but only to the extent that the mechanism(s) of action are known for the reference product. In FDA's draft Guidance for Industry, "*Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (2012)*," we explain: "If the clinically relevant mechanism(s) of action are known for the reference product or can reasonably be determined, one or more of the functional assays should reflect these mechanisms of action to the extent possible." Accordingly in your BLA submission, provide functional assays, including mechanism(s) of action, comparing CT-P13 to the reference product (US-licensed Remicade) and include a justification that CT-P13 utilizes the same mechanism(s) of action as US-licensed Remicade. This data and information should not be limited to the "primary" mechanism of action if other mechanism(s) of action are known or can reasonably be determined. Provide a summary of the data under Module 2.6 ("Nonclinical Written and Tabulated Summaries") and Module 2.3 ("Quality Overall Summary") with a link to the relevant section(s) of Module 3.

### **Celltrion's Comment**

*We agree that we will assess the secondary mode of action using US-licensed Remicade and CT-P13.*

*As these studies require substantial time and resources to conduct, we propose to provide the data for induction of regulatory macrophages and wound healing during the review cycle.*

*The quantity of radiolabelled material to be used within a lab is limited on a yearly basis by the Korean authorities. Since radiolabelled material is required for the macrophage induction assay (MLR assay (T-cell suppression)) the conduct of this assay is constricted by these regulations and data would not be available during the review cycle.*

*We therefore propose to only provide data from the induction of regulatory macrophages and wound healing assays. Does the FDA agree with the proposal?*

*We intend to include all data relevant to the mode of action(s) in Module 3. A summary table of the data will be included in both Modules 2.6 and 2.3. Is this approach acceptable?*

### **Meeting Discussion**

**Celltrion agreed to assess more than the "primary" mechanism(s) of action and proposed to provide data for two assays (induction of regulatory macrophages and wound healing) at**

the mid-cycle review time point. However, Celltrion noted that a third study, the MLR assay, will be a challenge to complete due to restrictions on the use of necessary radioactive reagents, and, if conducted, the results would not be available during the review cycle. Celltrion asked if the induction of regulatory macrophages could serve as a surrogate for the MLR, as they are redundant. FDA responded that whether the MLR assay was necessary based on redundancy in testing with another assay would be a review issue based on the data provided and Celltrion's justification.

FDA reminded Celltrion that a 351(k) application for a proposed biosimilar product is required to include information demonstrating that the proposed biosimilar product and the reference product utilize the same mechanism or mechanisms of action for the condition(s) of use for which licensure is sought, but only to the extent that the mechanism(s) of action are known for the reference product or can reasonably be determined. FDA reiterated that Celltrion should address any other mechanism(s) of action of the products in the other conditions of use for which Celltrion is seeking licensure, given that Celltrion is proposing to extrapolate to other conditions of use for which US-licensed Remicade was licensed. Celltrion should provide a comprehensive justification that their proposed combination of functional assays reflects all mechanisms of action that underlie the activity of the proposed biosimilar and the reference product in the conditions of use for which Celltrion is seeking licensure.

In addition, FDA stated that an application is expected to be complete at the time of submission, and any materials submitted later may not be reviewed during the review cycle.

#### Post-meeting Addendum

FDA acknowledges the challenge as described by Celltrion with conducting the MLR assay. However, FDA believes that these barriers are not insurmountable as there are other assays that can evaluate this activity and do not require radiolabelled material. Therefore, FDA recommends that all three assays discussed at the meeting be performed as part of Celltrion's approach to demonstrate that its proposed biosimilar has the same mechanism(s) of action as the reference product, to the extent the mechanism(s) are known or can reasonably be determined. The submission of this information should be in the original 351(k) BLA. If Celltrion chooses to submit the results from two assays only (induction of regulatory macrophages and wound healing), this would be at Celltrion's risk and would be a review issue. If Celltrion chooses such an approach, a justification should be submitted as to why the MLR assay is not needed to support a demonstration that its proposed biosimilar has the same mechanism(s) of action as the reference product beyond the feasibility rationale put forth during the meeting.

## CLINICAL

### Question 14

*The clinical data supporting the biosimilarity of CT-P13 and US-licensed Remicade® will be based on three pivotal studies, with additional studies provided as supporting data. These studies include:*

- *CT-P13 1.1 comparing CT-P13 and EU-approved Remicade® in patients with Ankylosing Spondylitis with PK similarity as the primary endpoint and additional PK attributes, PD, safety and efficacy over 54 weeks as secondary endpoints;*
- *CT-P13 3.1 comparing CT-P13 and EU-approved Remicade® in patients with Rheumatoid Arthritis with therapeutic equivalence based on ACR20 at Week 30 as primary endpoint and additional efficacy, safety, PD and PK as secondary endpoints over 54 weeks;*
- *CT-P13 1.4, a 3-way PK similarity study in healthy volunteers comparing CT-P13, EU-approved Remicade® and US-licensed Remicade®; this study together with 3-way CMC comparative data are intended to provide a bridge to clinical data generated in studies CT-P13 1.1 and 3.1 which used only EU-approved Remicade® as the comparator.*
- *CT-P13 1.3, an extension of study CT-P13 1.1, in which AS patients on Remicade® were switched to CT-P13 for a further 12 months and patients originally assigned to CT-P13 remained on this treatment for a further 12 months;*
- *CT-P13 3.2, an extension of study CT-P13 3.1 in which RA patients on Remicade® were switched to CT-P13 for a further 12 months and patients originally assigned to CT-P13 remained on this treatment for a further 12 months;*

*Other smaller studies which provided pilot data (study CT-P13 1.2, in 19 RA patients from Philippines); local data (Study CT-P13 3.3 in 15 RA patients in Russia and Study B1P13101, Phase 1/2: Study in 108 RA patients in Japan) and preliminary post-marketing data will be provided as supportive data.*

*CELLTRION considers that these studies are sufficient to supplement the extensive physicochemical, biological, and non-clinical data in support of the licensing of CT-P13 as a biosimilar to US-licensed Remicade® under Section 351(k) of the Public Health Service Act.*

*Does the FDA agree?*

#### **FDA Response**

If the results of study CT-P13 1.4, along with the noted 3-way analytical similarity data, can, among other things, adequately establish a scientific bridge to justify the relevance of the data obtained using EU-approved infliximab, the listed studies may be sufficient to support a demonstration of no clinically meaningful differences between CT-P13 and US-licensed Remicade. However, the adequacy of the data will be a review issue.

#### **Meeting Discussion**

**This question was not discussed.**

#### **Question 15A**

*CELLTRION has developed and validated assays to assess Anti-Drug Antibodies (ADA) and neutralizing antibodies (NAb) intended to be used in the CT-P13 clinical trials. CELLTRION*

*has taken a multi-tiered approach to the testing of patient samples for immunogenicity, which involved a rapid sensitive screening assay followed by a confirmatory assay. If positive in the confirmatory assay, samples were further characterized in the neutralizing antibody assay. Of note, a conservative approach of using normal human serum rather than patient serum for establishing a cutoff value for the assays has been used.*

*Does the FDA agree with this testing and validation approach?*

### **FDA Response**

Your proposal to use a step-wise approach for the assessment of ADA and neutralizing antibodies is reasonable. However, the use of a cutoff value for the assay based on samples from healthy volunteers has the potential of increasing the rate of false positive results, which underestimates and reduces the ability to detect potential differences in immunogenicity between CT-P13 and EU-approved infliximab in the target patient population, if differences exist. Therefore, the cutoff value for the validated screening assay should be based on background levels determined in the target population (i.e., rheumatoid arthritis patients). Refer to Shankar et al., Journal of Pharmaceutical and Biomedical Analysis 48 (2008), 1267-1281 and the draft Guidance for Industry, “Assay Development for Immunogenicity Testing of Therapeutic Proteins” for important aspects of immunogenicity assay development. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf>

### **Celltrion’s Comment**

*The choice of the current cutoff was set in line with FDA guidance on evaluation of immunogenicity of therapeutic proteins (recommended range of false-positive should not exceed 5%).*

*During the development of the ADA screening assay, cut points using both RA serum and normal serum were explored. Data showed that the cut point factor using RA serum was higher than that using normal serum (e.g. 1.98 and 1.73 respectively).*

*The most conservative approach was applied, which was using normal serum with the lower cut point. As pointed out by FDA this could increase the probability of false positive samples but it would minimize false negatives. Any false positive samples from the screening assay would be identified via the neutralizing assay. Since virtually all ADAs are neutralizing in nature (96.7 – 100% in the weeks 14, 30 and 54 samples) the neutralizing assay can be considered as a confirmatory assay as well.*

*It is noted that out of 602 samples tested at baseline only 15 (<2.5%) measured positive in the screening and 5 (<1%) by the neutralizing assay.*

*At this point it would not be possible to analyze samples using a cut point established with sera from an RA patient as the study is now complete, and there is paucity of retained samples. In summary, regardless of selected cutoff values, it is anticipated that no clinically meaningful differences in immunogenicity will be observed since the cut points are close and a two assay format is effectively applied.*

### **Meeting Discussion**

As summarized in Celltrion's comment above, Celltrion stated the choice to use serum from healthy volunteers, rather than from patients with RA, to establish the cutoff value for the assay was due to the lower cutoff value with the intent to minimize false negative results. Celltrion added that the cutoff values determined from serum of both healthy volunteers and RA patients were quite close. Only 15 out of 602 patient samples tested positive, and the data did not suggest false positive results.

FDA acknowledged that Celltrion's study was complete, and that samples were not available for re-testing. FDA advised Celltrion to provide a detailed justification for how using a cutoff value based on serum from healthy volunteers would be applicable to an immunogenicity assessment in patients with RA.

FDA noted that Celltrion's approach was not consistent with the recommendations in the draft guidance, which is to calculate the cutoff value using sera from the patient population to be studied. However, Celltrion's approach generally seemed reasonable given that the data showed that the cutoff values were within a narrow range of each other, and Celltrion should submit a detailed justification to support use of the sera from healthy volunteers. In addition, FDA noted that there are other confounding factors associated with the RA patient population such as the presence of rheumatoid factor and other auto-antibodies, and concomitant treatment with methotrexate and other immunosuppressants, which should be addressed in Celltrion's justification. FDA added that an increase in either the proportion of false negatives or false positives would tend to bias the results toward the alternative hypothesis of no differences in immunogenicity between the products.

Celltrion maintained that the approach they used was conservative but agreed to provide further justification.

### **Question 15B**

*In addition, analysis of antibodies (both neutralizing and non-neutralizing) as well as the titer for ADA and NAb in the pivotal studies CT P13 3.1 and CT P13 1.1 were conducted and will be provided in the BLA. Furthermore, impact of ADA/Nab including titer data on efficacy and safety were assessed in pivotal studies. There was an apparent correlation for presence or absence of antibodies with clinical efficacy and safety. However, the assessment failed to confirm any trend with regard to ADA/Nab titer and the efficacy/safety of CT-P13 or EU-approved Remicade. For the extension studies CT P13 3.2 and CT P13 1.3, titer analysis is not considered valuable to assess the trend or impact of titer considering limited dataset compared to the pivotal studies. Therefore, the presence of antibodies will be assessed without measuring titer for extension studies CT-P13 3.2 and CT-P13 1.3.*

*Does the FDA agree?*

### **FDA Response**

Your proposal appears reasonable.

### **Meeting Discussion**

**This question was not discussed.**

#### **Question 16**

*In study CT-P13 3.1, the mean joint damage score decreased from baseline at Week 54 in each treatment group. Although the mean decreases from baseline were similar in the CT-P13 and EU-approved Remicade® treatment groups, they were larger than those previously reported for Remicade®. Further investigations demonstrated that the evaluation of joint damage progression was different from the method employed in ATTRACT study. Subsequently, CELLTRION has conducted a re-evaluation of the radiographs, using an approach similar to that used in the ATTRACT study, i.e. using van der Heijde modification of the Sharp scoring system. The reevaluation showed that the changes in progression scores in the CT-P13 and EU-approved Remicade® groups in study CT-P13 3.1 were similar to the changes noted in the ATTRACT study. Moreover, the re-evaluated result confirmed the initial evaluation showing similar results for the CT-P13 and the EU-approved Remicade® groups. In light of this information, CELLTRION is not planning to do a similar re-evaluation in the extension study CT-P13 3.2 and hence joint damage progression data in the BLA will only include the initial comparative evaluation between the two treatment groups.*

*Does the FDA agree?*

#### **FDA Response**

Your proposal seems reasonable.

### **Meeting Discussion**

**This question was not discussed.**

#### **Question 17**

*The number of patients included in the safety analysis for CT-P13 exceeds the recommended long-term exposure guidelines in ICH E1A. CELLTRION consider that the robust analyses, and number of patients exposed to CT-P13 is sufficient to assess the long term safety and immunogenicity of the product.*

*Does the FDA agree?*

#### **FDA Response**

While the size of the proposed safety database appears reasonable, the acceptability of the evaluation of the safety and immunogenicity in non-treatment naïve patients who undergo a single transition from EU-approved infliximab to CT-P13 will be a review issue.

We note that a control arm of patients who remain on the comparator product (i.e., EU-approved infliximab) to permit a contemporaneous comparison would be the ideal design. Whether the data from study CT-P13 3.2 which compared patients who remained on CT-P13 to those who underwent a single transition from EU-approved infliximab to CT-P13 is adequate will be a review issue. See also FDA's response to Question 22, comment 3.

**Meeting Discussion**

**This question was not discussed.**

**Question 18**

*CELLTRION's current understanding is that the safety profile of CT-P13 along with substantial achievement of biosimilarity based on analytical, animal and clinical similarity data supports labeling and routine pharmacovigilance practices without a formal risk evaluation and mitigation strategy. CELLTRION is proposing to develop a medication guide for patients and focused communication strategy with health care providers in relation to specific safety risks and concerns in a similar fashion with the previously approved REMS for US-licensed Remicade®. Assuming the Division's review of safety is similar.*

*Does the FDA agree with this approach?*

**FDA Response**

In August 2011, FDA released Remicade from its previously approved REMS and determined that "maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1" (see August 1, 2011, letter, available at Drugs@FDA). Accordingly, at this time, we agree that developing a Medication Guide for patients would be appropriate for your proposed biosimilar product.

We intend to make a final determination for the need for a REMS and/or Medication Guide during the review of your application.

**Meeting Discussion**

**This question was not discussed.**

**Question 19**

*CELLTRION is planning to* [REDACTED] (b) (4)

*Does the FDA agree with this approach?*

**FDA Response**

No, we do not agree. [REDACTED] (b) (4)

**Meeting Discussion**

**This question was not discussed.**

**Question 20**

*CELLTRION has generated an overwhelming body of analytical and in vitro functional data to support biosimilarity and extrapolation across all indications; based on this and the data generated in the clinical trials described under Q14 in both RA and AS patients, CELLTRION is seeking to gain approval for all conditions for which Remicade® is approved in the US. CELLTRION is planning to submit additional safety and efficacy data from IBD patients included into Korean PMS registry as additional information to support extrapolation to IBD indications.*

*Does the FDA agree that the current data package could be acceptable for review to support approval for all currently licensed conditions of use for Remicade®?*

**FDA Response**

In the BLA data package provide (1) sufficient information to support a demonstration of biosimilarity in an appropriate condition(s) of use, and (2) sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which you seek licensure. This justification may include the additional clinical data from the IBD registry. See also see FDA's response to Question 16 from the July 10, 2013 BPD Type 3 meeting for additional information. The adequacy of the data and the justification for extrapolation will be a review issue.

**Meeting Discussion**

**This question was not discussed.**

**REGULATORY**

**Question 21**

*CELLTRION is specifically planning to address the biosimilarity assessment concerns arising out of analytical, animal and clinical similarity data gathered in the course of development of CT-P13 as the proposed biosimilar to US-licensed Remicade® with a tabular presentation of issues (Table 1 and Table 2), scope of uncertainty, impact on PK, PD, Efficacy and Safety, and supportive data to reduce/minimize the uncertainty. This discussion will reside in module 2 clinical summaries and reviewer's guide, as appropriate.*

*Does FDA agree with this approach?*

**FDA Response**

The approach to place the listed information in Module 2 as appropriate is reasonable.

**Meeting Discussion**

**This question was not discussed.**

## **Question 22**

*Does the FDA have any other recommendations or requests regarding format or content of this BLA submission?*

## **FDA Response**

We have the following recommendations regarding format or content for your BLA submission:

1. **Format of Adverse Events (AEs) presentation:** The format for safety presentation of the Integrated Summary of Safety, as proposed in Celltrion's submission dated April 4, 2014, referred to only the AEs of special interest. It is unclear whether the same format will be used for the remainder of the safety data presentation, i.e., all AEs, AEs leading to discontinuation, SAEs, etc. We recommend that you use the same format throughout the safety data presentation.
2. **Integrated Summary of Safety:** You propose to provide descriptive safety, including events of special interest (ESIs) from all studies in RA and AS as individual study reports. This proposal is reasonable.

In the "Proposed Safety Table Outline for CT-P13 BLA Submission", you propose to present a summary of ESIs according to the following groups: controlled RA data (CT-P13 1.2, CT-P13 3.1, CT-P13 3.3 and B1P13101); uncontrolled RA data (CT-P13 1.2 and 3.2); pooled data from "all studies" which is shown on the tables as "AS+RA". However, you state on page 253 of your submission that you do not plan to integrate studies CT-P13 1.2, CT-P13 3.3 and B1P3101 into the safety analyses, which contradicts the information presented in the table. In addition, you present analyses in Section 12.3.1.4 of your submission (Adverse Events of Special Interest), where you have pooled only controlled studies CT-P13 3.1 and CT-P13 1.1. Clarify the studies you intend to include in your pooled analyses.

We agree with your proposal to present data individually and as pooled data. However, because of the differences in study patient populations and dosing regimens, we are concerned about the limitations of simple pooling of this data. Therefore, we recommend that for the pooled safety analysis you propose an approach to account for the differences in the study designs, e.g., by conducting a meta-analysis of the study-specific estimated differences between groups with respect to specific AEs or by adjusting for study. See also FDA's response to Question 19.

## **Celltrion's Comment for FDA Response 1 and 2**

*We acknowledge FDA's comments and CELLTRION would like to clarify the following:*

- a. *We are in agreement that there are inherent limitations in integrating all completed CT-P13 studies due to difference in design, patient population, dose level, concomitant medication use and region.*
- b. *Therefore to facilitate FDA review, our plan is to present all reported TEAEs, AEs leading to discontinuation and SAEs per individual study in 5.3.5.3, without integrating across studies and indications.*

- c. *For ESIs we are planning to present pooled analyses which will allow review by individual studies and across all studies and indications. Furthermore, it will be presented in the same table format as that submitted in the April 4th Submission package.*
- d. *Since electronic datasets for the Japanese study B1P13101 are not accessible, the safety data will be presented separately in its own CSR, without integrating with other studies.*

### **Meeting Discussion**

**Celltrion clarified the proposal for submitting the safety data as summarized in their comments. The Sponsor further proposed that in addition to presenting the safety from each study separately and pooled, that they would conduct a meta-analysis of the study-specific estimated differences between groups with respect to specific AEs in order to account for the differences in the study designs. FDA stated that this proposal was reasonable. FDA acknowledged Celltrion's proposal to present the safety data from the Japanese study B1P13101 in its own clinical study report without the electronic datasets and stated that the adequacy of these data would be a review issue.**

3. Assessment of safety and immunogenicity for non-treatment naïve patients who undergo a single transition from EU-approved infliximab to CT-P13: For this assessment, you propose to compare the data from patients who undergo a single transition from EU-approved infliximab to CT-P13 to those who continue on CT-P13 (maintenance) from extension study CT-P13 3.2. This approach does not compare patients who transition from EU-approved infliximab to CT-P13 with patients continuing on EU-approved infliximab, which is the comparison of interest. This approach also may be confounded by differences in completer subsets and residual differences due to the different double-blind treatments. Therefore, we also request that you provide a comparison of the safety and immunogenicity rates in the same patients before and after the transition (although this analysis also has limitations). See also FDA's response to Question 17.

### **Celltrion's Comment**

*We acknowledge FDA response, part 3 on patients undergoing switch to CT-P13 and will duly address the recommendation by presenting a comparative table of safety and immunogenicity rates in the same patients, before and after the transition accompanied with discussion on limitations of this approach.*

### **Meeting Discussion**

**This question was not discussed.**

4. Equivalence Margin: We do not agree with your approach in selecting an equivalence margin. The equivalence margin should be informed by considerations in the draft Guidance for Industry, "Non-Inferiority Clinical Trials." In particular, the proposed margins should be based on all relevant adequate and well-controlled trials and should preserve at least 50% of the estimated lower confidence bound of the treatment effect of the reference product. Include a justification that the 95% confidence interval for the estimated difference in Week 30 ACR20 response probabilities from Study CT-P13 3.1 is able to rule out an appropriately justified margin.

### **Celltrion's Comment**

*We acknowledge your comments in regards to equivalence margins and we will follow your recommendation in justification of equivalence margins in 2.7.3.*

### **Meeting Discussion**

Celltrion agreed to provide a justification for the selection of the equivalence margin, but asked if uncontrolled studies, e.g., registry data could be included. FDA responded that only randomized controlled trials in patient populations reflective of the tested population should be included to support the expected treatment effect of the reference product, and the subsequent selection of the margin for the comparative clinical study. Celltrion asked if studies should be excluded when the patient population is known to be different from the patients to be enrolled in the comparative clinical study. FDA responded that while this is the recommended approach, the Sponsor could justify that the addition of other studies did not impact the treatment effect. Celltrion noted that they used absolute difference to determine the treatment effect and select the margins when designing the study per the advice of the EMA's CHMP. FDA noted that the preferred approach is to have an adequately justified, pre-specified equivalence margin. However, FDA also acknowledged that since Celltrion has already conducted their clinical studies, justification of the margins could only be provided post hoc. Celltrion agreed to provide justification that the primary analysis results would be able to rule out an appropriate equivalence margin.

5. Missing Data: In Study CT-P13 3.1, there is a considerable amount of missing data in analyses of continuous secondary efficacy endpoints with respect to the intention-to-treat estimand (e.g., an analysis of the difference between groups in the mean change from baseline in DAS28 at 30 weeks in all randomized patients, regardless of adherence to treatment or to the protocol). As recommended in the 2010 National Research Council report *The Prevention and Treatment of Missing Data in Clinical Trials*, explicitly define the causal estimand of interest that is being targeted by each analysis, and identify the assumptions of that analysis. Conduct sensitivity analyses to explore the potential impact of violations in assumptions about the missing data.

### **Celltrion's Comment**

*We acknowledge your comments on missing data and we will conduct DAS28 analysis in ITT patient population in CT-P13 3.1 study at week 30 in all randomized patients using sensitivity analyses to explore the impact of missing data imputation methods. Is that an acceptable approach?*

### **Meeting Discussion**

Celltrion stated that approximately 15% of patients dropped out by Week 30 in the RA study. To address the uncertainties with the missing data, Celltrion proposed to carry out analyses in the intent-to-treat (ITT) population at Weeks 15 and 30. The Sponsor also planned to conduct sensitivity analyses using Mixed-Effects Models for Repeated Measures, as well as various imputation models.

**FDA responded that Celltrion’s proposal was reasonable, but advised Celltrion to justify that the assumptions of each model about the missing data at week 30 are reasonable (with respect to an evaluation of the intent-to-treat estimand). Celltrion agreed to explore the reasons for and patterns of dropout and to provide justification that the results are sensitive to violations in assumptions about the missing data. FDA also recommended that a similar approach be used for the Health Assessment Questionnaire-Disability index (HAQ-DI) as a continuous efficacy endpoint and a key secondary endpoint which was not captured as part of DAS28.**

6. Additional Nonclinical Comment: If the similarity assessment between CT-P13 and US-licensed Remicade is judged to be adequate from a nonclinical perspective, additional evaluations examining safety pharmacology, reproductive toxicology, immunotoxicity, and carcinogenic potential will not be necessary.

**Celltrion’s Comment**

*No comment to this question.*

**Meeting Discussion**

**This question was not discussed.**

**Question 23**

*CT-P13, under the trade name [REDACTED]<sup>(b) (4)</sup>™, was approved by the EMA in 2013 with the same nonproprietary name “Infliximab” as currently used with Remicade®. CELLTRION proposes to keep the same nonproprietary name “Infliximab” for its biosimilar product, CT-P13, and will propose a trade name at the time of BLA submission.*

*Does FDA have any additional guidance regarding labeling, specifically the naming of the active ingredient?*

**FDA Response**

At this time, FDA cannot provide additional information regarding the nonproprietary name of your proposed biosimilar product. FDA anticipates that additional information will be provided to you at an appropriate time during the review of your BLA.

With respect to your draft proposed labeling for CT-P13, it would be reasonable to incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications, as a starting point. Submit your draft proposed labeling for CT-P13 in PLR format. We request that your annotated labeling identify, with adequate specificity, the source of all data and information presented. We will provide additional comments on draft proposed labeling during review of your BLA.

**Meeting Discussion**

**This question was not discussed.**

**Question 24**

*CELLTRION plans to submit*

(b) (4)

*Does the FDA agree?*

**FDA Response**

No, we do not agree. In our August 9, 2013 meeting minutes for the July 10, 2013 BPD Type 3 meeting held with you, we included a post-meeting note that provided further information about the required initial PSP. We stated, in part: “FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (PSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed PSP prior to the submission of your planned 351(k) BLA.... Sections 505B(e)(2)(C) and 505B(e)(3) set forth a process lasting up to 210 days for reaching agreement with FDA on an initial PSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the initial PSP... After the initial PSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by FDASIA. 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.” The meeting discussion for question 19 at the July 10, 2013, meeting states: “Regarding timing of submission of the PSP, FDA advised Celltrion to submit their PSP as soon as possible based on Celltrion’s assertion that they have completed their clinical development program except for the 3-way PK similarity study.” We reiterate our recommendation to submit an initial PSP as soon as possible, and in advance of submission of your proposed BLA.

We also refer you to the draft Guidance for Industry entitled “*Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*” (July 2013), which explains that “[if] a phase 3 study, or a combined phase 2 and phase 3 study, will not be conducted, the sponsor should submit the initial PSP no later than 210 calendar days before a marketing application or supplement is submitted.”

FDA cannot commit to spending less than 90 days to provide initial comments on your iPSP, or less than 30 days to confirm agreement with your agreed iPSP. However, it should be noted that you may opt to spend less than 90 days for review of our comments on your iPSP and submission of your agreed iPSP. You should submit an *agreed and confirmed* pediatric study plan with your BLA submission.

Your proposal to

(b) (4)

would not be appropriate for CT-P13. To address PREA, you should consider, among other things, the indications for which US-licensed Remicade is licensed and where a justification for extrapolation across biological products (i.e., from the reference product to the proposed biosimilar product) could be provided in the context of your biosimilar development program. We note that Remicade has unexpired orphan exclusivity for pediatric

ulcerative colitis; [REDACTED]

(b) (4)

### **Celltrion's Comment**

*We acknowledge your comment. We would like to report that we have submitted the iPSP on 25 April 2014.*

*The Sponsor would like to acknowledge the slight delay in submitting the PSP relative to BLA submission timeline. Our current plan is to submit the BLA in mid-July 2014. Based on this information, will this create any issue in terms of filing the BLA?*

### **Meeting Discussion**

**Celltrion commented that the iPSP was submitted on April 24, 2014, and Celltrion's current plan was to submit the BLA in mid-July. Celltrion noted that 90 days for FDA review of the iPSP from the April submission date would bring the timeline to July, which was when they planned to submit their BLA. Celltrion asked whether inability to secure an agreed iPSP by July posed any issues with the planned timing of their BLA submission.**

**FDA responded that guidance regarding submission of the iPSP was provided in the August 9, 2013 meeting minutes. FDA stated further advice regarding the specific issue related to timing would be provided in a post-meeting addendum.**

### **Post-Meeting Addendum**

**At the BPD Type 4 meeting, Celltrion advised that they had submitted an iPSP on April 24, 2014, and asked whether the delay in submitting the iPSP would create any issues in terms of filing its planned 351(k) BLA (intended for submission in mid-July 2014). As noted above, Celltrion's iPSP submission in late April 2014 does not provide adequate time to reach agreement with FDA on the proposed PSP prior to the planned submission of Celltrion's 351(k) BLA in mid-July 2014 (see August 9, 2013, meeting minutes describing a process lasting up to 210 days for reaching agreement with FDA on an iPSP).**

**Section 505B(e)(1) of the Federal Food, Drug, & Cosmetic Act (FD&C Act) provides that an applicant shall submit an iPSP prior to submission of the pediatric assessments described under section 505B(a)(2) of the FD&C Act. As noted above, the iPSP was submitted on April 24, 2014. At this time, the lack of an agreed PSP for this proposed 351(k) BLA would not, on its own, preclude filing of an otherwise acceptable 351(k) BLA submission. However, it should be noted that a 351(k) applicant is required to submit the pediatric assessments described in section 505B(a)(2) of the FD&C Act with the application (see, e.g., section 505B(a)(1) and 505B(m) of the FD&C Act). Among other things, the iPSP and pediatric assessments are expected to address all the indications for which you are seeking licensure. We encourage you to review our comments on your iPSP prior to submission of the pediatric assessments with your 351(k) application.**

**As noted above, FDA cannot commit to spending less than 90 days to provide initial comments on your iPSP, or less than 30 days to confirm agreement with your agreed iPSP.**

**However, we reiterate that you may opt to spend less than 90 days for review of our comments on your iPSP and submission of your agreed iPSP.**

**Question 25**

*Does the Division anticipate that an Arthritis Advisory Committee would be convened as part of the BLA review process? If so, does the Division have any guidance on when during the review process an Advisory Committee meeting would be convened?*

**FDA Response**

Given the complexities of the application, it is likely that an Advisory Committee meeting will be convened. However, a final determination on the need for an Advisory Committee meeting will be made after the BLA submission, and until this determination is made we cannot provide further guidance on the timing of the meeting.

**Meeting Discussion**

**This question was not discussed.**

**Question 26**

*In CELLTRION's view, as long as pertinent product quality information is shared with the originator to enable them to review all potential 351k patents to determine whether they want to challenge any of them, that should be adequate and there is no need to submit the entire BLA. Does FDA concur with this view? If so, can the FDA provide specifics on the type and extent of information to be shared with the originator?*

**FDA Response**

Section 351(l)(2)(A) states that a biosimilar applicant "shall provide to the reference product sponsor a copy of the application submitted to the Secretary under subsection (k), and such other information that describes the process or processes used to manufacture the biological product that is the subject of such application."

FDA has not taken a position on the scope of this provision.

**Meeting Discussion**

**This question was not discussed.**

**Question 27**

*Does the FDA allow a single Biologic License Application for a [REDACTED] (b) (4) [REDACTED] ?*

**FDA Response**

Whether your product [REDACTED] (b) (4) will be a review issue and we will give careful consideration to any safety issues this may raise.

[REDACTED] (b) (4)

**Meeting Discussion**

**This question was not discussed.**

**ADDITIONAL QUESTIONS**

- *What is the total time from submission to decision (2+10=12 months or 10 months)*

**Meeting Discussion**

**FDA confirmed that the 351(k) BLA would have a standard review, which is 10-months as agreed to as part of BsUFA. Celltrion also inquired about the timing of an Advisory Committee (AC) meeting and the Late Cycle meeting. FDA responded that the AC meeting is usually held around month 8 of the review cycle per the 21<sup>st</sup> Century Review initiative, and that this application would not have a Late Cycle meeting as the product would not qualify for “The Program” under PDUFA.**

- *Are FEI numbers required at time of submission or will a DUNS number be acceptable?*

### **Meeting Discussion**

**Celltrion commented that all facilities will be ready for inspections at the time of the BLA submission. However, some facilities may not have the registration numbers or the FEI numbers at the time of inspection. Celltrion added that the process is underway to obtain the FEI numbers for these facilities. Celltrion asked if not having the FEI numbers at the time of the BLA would pose any problems. FDA responded that additional advice would be provided as a post-meeting addendum in the meeting minutes.**

### **Post-Meeting Addendum**

**FEI numbers are not required at the time of BLA submission, but would be required before licensure.**

## **3. DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed. FDA advised Celltrion to submit a complete BLA application.

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

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

## **4. PREA PEDIATRIC STUDY PLAN**

Under the Pediatric Research Equity Act [section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355c)], all applications for new active ingredients, 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(m) 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 or deferred.

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (PSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed PSP prior to initiating your comparative clinical study (see additional comments below regarding expected review timelines).

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 initial PSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the initial PSP. The initial PSP must include an outline of the pediatric study or studies that a sponsor plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); and any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation. After the initial PSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by FDASIA (see section 505B(e) of the FD&C Act and FDA's Guidance for Industry on Pediatric Study Plans: *Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>). 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.

## **5. PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements of Prescribing Information](#) website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents, and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

## **6. MANUFACTURING FACILITIES**

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

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

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided

in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

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

Corresponding names and titles of onsite contact:

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

**7. ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

**8. ACTION ITEMS**

There were no action items.

**9. HANDOUTS**

Handouts used during the meeting discussion are attached.

## **IND 118135: CT-P13 BPD Type 4 Meeting**

### **CELLTRION RESPONSE TO FDA PRELIMINARY RESPONSE**

In reference to the preliminary responses to CELLTRION's questions provided by the Agency for IND 118135, CELLTRION provides the following responses and would like to discuss the following subset of the FDA responses. The questions are listed below in the preferred order of discussion.

#### **ORDER OF QUESTIONS**

##### *CMC:*

Question 1  
Question 8  
Question 9  
Question 13  
Question 6

##### *Clinical*

Question 15A  
Question 22  
Question 24

##### *CMC*

Question 12

##### *Additional questions*

### **CHEMISTRY, MANUFACTURING AND CONTROLS**

#### **QUESTION 1**

Does the Agency agree that the proposed bioassay is adequate for controlling drug substance and drug product bioactivity in support of the CT-P13 BLA submission and that a bioassay to control Fc-mediated functionality is not needed?

#### **FDA Response**

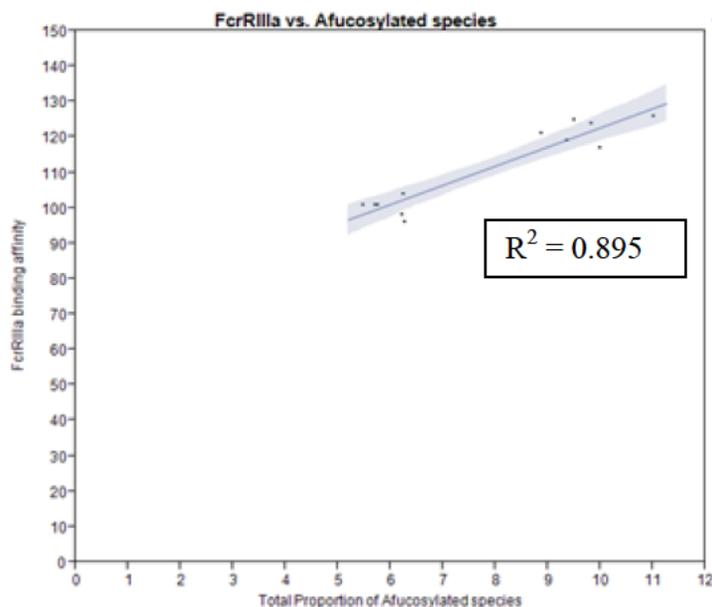
The proposed cell-based bioassay appears appropriate for the intended purpose of assessing target-binding activity. However, the detailed procedure and adequacy of the validation will be a review issue.

An assay is still needed to ensure that Fc-mediated functions such as ADCC remain in control. While acceptance criteria for afucosylated glycoforms level could be an appropriate strategy to control changes in effector function such as ADCC, there may be other biochemical aspects by which ADCC and other effector activities could be affected which are not reflected by assessing and controlling afucosylation only.

A validated assay evaluating Fc function, including ADCC or FcγRIIIa binding with quantitative specifications for release testing is expected to be provided in the BLA submission.

### Sponsor Response

A validated assay evaluating the Fc effector function, FcγRIIIa binding with proposed quantitative specifications of (b)(4) % will be included in the drug substance specifications. However, considering that there is a clear correlation between afucosylation levels and FcγRIIIa binding as seen in Figure 1, (b)(4)



**Figure 1: A Scatter Plot Showing Percent Afucosylated Glycan Species and FcγRIIIa Binding (n=12; 6 each CT-P13 and EU-approved Remicade®)**

Data derived from IND amendment submitted on 06 February, 2014:

Table 3.2.R-135: Summary of Afucosylation, FcγRIIIa Binding Affinity, ADCC (w/normal PBMC and NK cells) and CDC in CT-P13 and EU-approved Remicade® Batches.

Figure 3.2.R-62: A Scatter Plot Showing Percent Afucosylated Glycan Species and FcγRIIIa Binding

### **QUESTION 8**

As discussed during the BPD Type 3 meeting held on 10 July 2013, the following categories of new data have been generated in the enhanced 3-way quality similarity assessment and are summarized in this Briefing Document:

- Physicochemical analysis
- A full complement of Fc receptor and antigen binding assays (i.e., the SPR analytical methods used in the 2-way similarity study) were conducted including FcγRIIIa binding
- The NK cell ADCC assay results are included

- The LPS-stimulated monocytes ADCC assay
- Main mechanism of action study, including apoptosis, and reverse signaling

Does the FDA concur that all recommended studies have been conducted in an effort to demonstrate similarity of CT-P13 with US-licensed Remicade<sup>®</sup> and EU-approved Remicade<sup>®</sup>? Based on the quality data provided, does the FDA concur that the 2-way analytical similarity assessment has adequately demonstrated similarity of CT-P13 to EU-approved Remicade<sup>®</sup> and that with the bridge established by the 3-way similarity assessment of the analytical data with US-licensed Remicade<sup>®</sup>, CT-P13 qualifies for a biosimilar program versus US-licensed Remicade<sup>®</sup> under Section 351(k) of the PHS Act?

### **FDA Response**

We acknowledge the enhanced 3-way analytical similarity program intended to provide more robust and complete analytical similarity data directly comparing CT-P13 with the reference product, US-licensed Remicade, and assess the analytical differences identified and discussed during the July 10, 2013 BPD Type 3 meeting. We note that differences between CT-P13 and US-licensed Remicade with respect to binding to FcγRIIIa, the relative percentage of afucosylated glycans, and ADCC activity remain. The adequacy of the data, including any justifications, and final acceptability of the assays and their validation, will be a review and/or inspectional issue, based upon the totality of the data submitted in the BLA.

We cannot make a determination as to whether analytical similarity has been adequately demonstrated between CT-P13, US-licensed Remicade, and EU-approved infliximab (the latter for purposes of evaluating the relevance of comparative data with EU-approved infliximab to an assessment of biosimilarity to US-licensed Remicade) without review of the full data package, which should include primary data (e.g., sensograms, gel images, chromatograms, etc.) and not only summary data.

### **Sponsor Response**

*We agree to include primary data from the similarity studies. We propose to include primary data from [REDACTED]<sup>(b)(4)</sup> of CT-P13, US-licensed Remicade<sup>®</sup> and EU-approved Remicade<sup>®</sup>. All other primary data will be available on-site during inspection.*

*Does the FDA agree with this plan?*

*We have conducted an extensive battery of qualification studies for all the characterization methods. We intend to provide method description and qualification summary tables for assays used for characterization of similarity. For methods used for similarity assessments which are also used for release testing, a cross-reference will be provided to 3.2.S.4.3 and 3.2.P.5.3, as appropriate. The full qualification reports are available upon request and/or during inspection. Does the FDA concur with this approach?*

*We would like to inform the FDA that it is not feasible to fully qualify certain characterization assays whilst qualification has been completed for the assays considered most critical.*

*Dose-response curve confirmed, but additional qualification was not feasible:*

- *ADCC using whole blood (inherent variability in whole blood from different donors)*
- *Macrophage induction (inherent variability)*

- *Suppression of T-cell proliferation (inherent variability)*

Assay qualification was not feasible:

- *ADCC using LPS-stimulated monocytes as target cells and PBMC as effector cells (no response from LPS-stimulated monocytes; appropriate positive and negative controls were included in the studies)*
- *Wound healing (inherent variability, qualitative assay, negative control: no wound healing was observed from non-regulatory macrophages)*

**QUESTION 9**

As discussed during the BPD Type 3 meeting held on 10 July 2013, enhanced 3-way similarity assessment data covering 7 additional batches of each product (CT-P13, US-licensed Remicade<sup>®</sup> and EU-approved Remicade<sup>®</sup>) has been provided including statistical analysis of variance. Does the FDA concur that together with the abridged 3-way similarity assessment data (which included 3 batches of each product) an adequate number of batches of each product have been tested to provide sufficient statistical power for the similarity assessment?

**FDA Response**

As discussed during the July 10, 2013 BPD Type 3 meeting in relation to Question 12, the number of lots tested and the statistical analysis should be adequately justified by CELLTRION. The adequacy of the analytical similarity assessment will be a review issue.

**Sponsor Response**

*Based on the outcome of the discussions during the BPD Type 3 meeting, the Sponsor has included analysis of an additional 7 batches of each product (CT-P13, US-licensed Remicade<sup>®</sup> and EU-approved Remicade<sup>®</sup>) including statistical analysis of variance. The data is provided in Table 22 and 23 (pages 113 and 114) of the Briefing Document.*

*Does the FDA agree with the statistical approach taken to evaluate the data (Bartlett's test and Welch's test for data showing significant difference in the Bartlett's test) or can you recommend an alternate statistical evaluation approach that may be more appropriate?*

*Does the FDA agree that if there is sufficient statistical power in the current analysis the number of batches selected for similarity assessment are adequate?*

**QUESTION 13**

Considering that the primary mechanism of action as well as critical Fc functionality were addressed using RP in the abridged 3-way assessment as well as tested further in the enhanced 3-way assessment, additional secondary studies (induction of regulatory macrophages, inhibition of T-cell proliferation and promotion of wound healing) using RP are considered unnecessary as they are not expected to be different from those already conducted using EU-approved Remicade<sup>®</sup>.

Does FDA concur?

**FDA Response**

Section 351(k)(2)(A)(i)(II) of the PHS Act requires that a 351(k) application for a proposed biosimilar product include information demonstrating that the proposed biosimilar product and

the reference product utilize the same mechanism or mechanisms of action for the condition(s) of use for which licensure is sought, but only to the extent that the mechanism(s) of action are known for the reference product. In FDA's draft Guidance for Industry, "*Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (2012)*," we explain: "If the clinically relevant mechanism(s) of action are known for the reference product or can reasonably be determined, one or more of the functional assays should reflect these mechanisms of action to the extent possible." Accordingly in your BLA submission, provide functional assays, including mechanism(s) of action, comparing CT-P13 to the reference product (US-licensed Remicade) and include a justification that CT-P13 utilizes the same mechanism(s) of action as US-licensed Remicade. This data and information should not be limited to the "primary" mechanism of action if other mechanism(s) of action are known or can reasonably be determined. Provide a summary of the data under Module 2.6 ("Nonclinical Written and Tabulated Summaries") and Module 2.3 ("Quality Overall Summary") with a link to the relevant section(s) of Module 3.

### **Sponsor Response**

*We agree that we will assess the secondary mode of action using US-licensed Remicade and CT-P13.*

*As these studies require substantial time and resources to conduct, we propose to provide the data for induction of regulatory macrophages and wound healing during the review cycle.*

*The quantity of radiolabelled material to be used within a lab is limited on a yearly basis by the Korean authorities. Since radiolabelled material is required for the macrophage induction assay (MLR assay (T-cell suppression)) the conduct of this assay is constricted by these regulations and data would not be available during the review cycle.*

*We therefore propose to only provide data from the induction of regulatory macrophages and wound healing assays. Does the FDA agree with the proposal?*

*We intend to include all data relevant to the mode of action(s) in Module 3. A summary table of the data will be included in both Modules 2.6 and 2.3. Is this approach acceptable?*

### **QUESTION 6**

Regarding shipping validation studies to support the BLA, CELLTRION proposes to summarize in the BLA two earlier shipping studies conducted to transport drug substance (b) (4)

These studies represent worst case scenario with regard to time and temperature excursions and mechanical shock during transportation. Additionally, the BLA will include a shipping validation protocol supporting air transportation (b) (4)

The US-specific validation data will be submitted in an amendment to the BLA during the review process.

Does the FDA agree with the proposed approach to address shipping validation to support the BLA submission and review?

### **FDA Response**

The proposed approach appears appropriate if Celltrion commits to providing the temperature profile during shipping validation studies. However, final assessment of particular shipping validation studies will be a review and inspectional issue.

### **Sponsor Response**

*The Sponsor proposes to include a single packaging configuration representative of the worst case configuration to accommodate various shipping configurations to different regions of the World.*



*his is considered worst case shipping conditions.*

*Does the FDA agree with the proposed shipping configuration for the shipping validation studies?*

### **QUESTION 12**

To address the residual risk due to the observed difference of near 23% in the FcγRIIIa binding, many different ADCC assays were undertaken with different effector and target cells during the enhanced 3-way assessment. Most importantly, when the most representative in vitro model for mimicking the in vivo environment (using LPS-stimulated monocytes as target cells), no ADCC activity was seen with CT-P13 or Reference Product (RP) or EU-approved Remicade<sup>®</sup>. Similar results were observed in the 2-way similarity assessment between CT-P13 and EU-approved Remicade<sup>®</sup> described in the IND 118135. Also, full complement of ADCC were repeated using RP to reaffirm the premise that ADCC is not considered a mechanism of action, which is also consistent with the data from public literature.

Does the FDA concur with CELLTRION that residual risk due to the differences in the ADCC assay results has been adequately addressed in the data generated from the abridged and enhanced 3-way similarity assessments?

### **FDA Response**

Whether the observed 23% difference in FcγRIIIa binding between EU-approved infliximab and CT-P13 was adequately addressed with the additional assessments will be a review issue based upon the totality of the data submitted for review in the BLA. In addition, as discussed during the July 10, 2013 BPD Type 3 meeting in relation to Questions 11 and 12, Celltrion should provide a robust analytical similarity assessment between CT-P13 and US-licensed Remicade, including an adequate analysis of any observed differences. The results of such an assessment will also be a review issue based upon the totality of the data submitted.

### **Sponsor Response**

*Following our BPD Type 3 meeting in July 2013, we have submitted additional data to support the abridged 3-way as well as the enhanced 3-way assessments. Please refer to Question 8 for the additional data provided.*

*In addition, the clinical data related to the MoA and extrapolation also discusses the effect of observed differences in FcγRIIIa binding on clinical efficacy and safety.*

*Does the FDA agree that the data provided from the enhanced 3-way similarity assessment facilitates the evaluation of the totality of evidence related to the absence of impact of FcγRIIIa binding on safety and efficacy?*

## **CLINICAL**

### **QUESTION 15A**

CELLTRION has developed and validated assays to assess Anti-Drug Antibodies (ADA) and neutralizing antibodies (NAb) intended to be used in the CT-P13 clinical trials. CELLTRION has taken a multi-tiered approach to the testing of patient samples for immunogenicity, which involved a rapid sensitive screening assay followed by a confirmatory assay. If positive in the confirmatory assay, samples were further characterized in the neutralizing antibody assay. Of note, a conservative approach of using normal human serum rather than patient serum for establishing a cutoff value for the assays has been used.

Does the FDA agree with this testing and validation approach?

### **FDA Response**

Your proposal to use a step-wise approach for the assessment of ADA and neutralizing antibodies is reasonable. However, the use of a cutoff value for the assay based on samples from healthy volunteers has the potential of increasing the rate of false positive results, which underestimates and reduces the ability to detect potential differences in immunogenicity between CT-P13 and EU-approved infliximab in the target patient population, if differences exist. Therefore, the cutoff value for the validated screening assay should be based on background levels determined in the target population (i.e., rheumatoid arthritis patients). Refer to Shankar et al., Journal of Pharmaceutical and Biomedical Analysis 48 (2008), 1267-1281 and the draft Guidance for Industry, “Assay Development for Immunogenicity Testing of Therapeutic Proteins” for important aspects of immunogenicity assay development.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf>

### **Sponsor Response**

*The choice of the current cutoff was set in line with FDA guidance on evaluation of immunogenicity of therapeutic proteins (recommended range of false-positive should not exceed 5%).*

*During the development of the ADA screening assay, cut points using both RA serum and normal serum were explored. Data showed that the cut point factor using RA serum was higher than that using normal serum (e.g. 1.98 and 1.73 respectively).*

*The most conservative approach was applied, which was using normal serum with the lower cut point. As pointed out by FDA this could increase the probability of false positive samples but it would minimize false negatives. Any false positive samples from the screening assay would be identified via the neutralizing assay. Since virtually all ADAs are neutralizing in nature (96.7 – 100% in the weeks 14, 30 and 54 samples) the neutralizing assay can be considered as a confirmatory assay as well.*

*It is noted that out of 602 samples tested at baseline only 15 (<2.5%) measured positive in the screening and 5 (<1%) by the neutralizing assay.*

*At this point it would not be possible to analyze samples using a cut point established with sera from an RA patient as the study is now complete, and there is paucity of retained samples.*

*In summary, regardless of selected cutoff values, it is anticipated that no clinically meaningful differences in immunogenicity will be observed since the cut points are close and a two assay format is effectively applied.*

## **QUESTION 22**

Does the FDA have any other recommendations or requests regarding format or content of this BLA submission?

### **FDA Response**

We have the following recommendations regarding format or content for your BLA submission:

1. Format of Adverse Events (AEs) presentation: The format for safety presentation of the Integrated Summary of Safety, as proposed in Celltrion's submission dated April 4, 2014, referred to only the AEs of special interest. It is unclear whether the same format will be used for the remainder of the safety data presentation, i.e., all AEs, AEs leading to discontinuation, SAEs, etc. We recommend that you use the same format throughout the safety data presentation.
2. Integrated Summary of Safety: You propose to provide descriptive safety, including events of special interest (ESIs) from all studies in RA and AS as individual study reports. This proposal is reasonable. In the "Proposed Safety Table Outline for CT-P13 BLA Submission", you propose to present a summary of ESIs according to the following groups: controlled RA data (CT-P13 1.2, CTP13 3.1, CT-P13 3.3 and B1P13101); uncontrolled RA data (CT-P13 1.2 and 3.2); pooled data from "all studies" which is shown on the tables as "AS+RA". However, you state on page 253 of your submission that you do not plan to integrate studies CT-P13 1.2, CT-P13 3.3 and B1P3101 into the safety analyses, which contradicts the information presented in the table. In addition, you present analyses in Section 12.3.1.4 of your submission (Adverse Events of Special Interest), where you have pooled only controlled studies CT-P13 3.1 and CT-P13 1.1. Clarify the studies you intend to include in your pooled analyses. We agree with your proposal to present data individually and as pooled data. However, because of the differences in study patient populations and dosing regimens, we are concerned about the limitations of simple pooling of this data. Therefore, we recommend that for the pooled safety analysis you propose an approach to account for the differences in the study designs, e.g., by conducting a meta-analysis of the study-specific estimated differences between groups with respect to specific AEs or by adjusting for study. See also FDA's response to Question 19.
3. Assessment of safety and immunogenicity for non-treatment naïve patients who undergo a single transition from EU-approved infliximab to CT-P13: For this assessment, you propose to compare the data from patients who undergo a single transition from EU-approved infliximab to CT-P13 to those who continue on CT-P13 (maintenance) from extension study CT-P13 3.2. This approach does not compare patients who transition from EU-approved infliximab to CT-P13 with patients continuing on EU-approved infliximab, which is the comparison of interest. This approach also may be confounded by differences in completer subsets and residual differences due to the different double-blind treatments. Therefore, we also request that you provide a comparison of the safety and immunogenicity rates in the same patients before and after the transition (although this analysis also has limitations). See also FDA's response to Question 17.
4. Equivalence Margin: We do not agree with your approach in selecting an equivalence margin. The equivalence margin should be informed by considerations in the draft Guidance for Industry, "*Non-Inferiority Clinical Trials*." In particular, the proposed margins should be based on all relevant adequate and well-controlled trials and should preserve at least 50% of the estimated lower

confidence bound of the treatment effect of the reference product. Include a justification that the 95% confidence interval for the estimated difference in Week 30 ACR20 response probabilities from Study CT-P13 3.1 is able to rule out an appropriately justified margin.

5. **Missing Data:** In Study CT-P13 3.1, there is a considerable amount of missing data in analyses of continuous secondary efficacy endpoints with respect to the intention-to-treat estimand (e.g., an analysis of the difference between groups in the mean change from baseline in DAS28 at 30 weeks in all randomized patients, regardless of adherence to treatment or to the protocol). As recommended in the 2010 National Research Council report *The Prevention and Treatment of Missing Data in Clinical Trials*, explicitly define the causal estimand of interest that is being targeted by each analysis, and identify the assumptions of that analysis. Conduct sensitivity analyses to explore the potential impact of violations in assumptions about the missing data.
6. **Additional Nonclinical Comment:** If the similarity assessment between CT-P13 and US licensed Remicade is judged to be adequate from a nonclinical perspective, additional evaluations examining safety pharmacology, reproductive toxicology, immunotoxicity, and carcinogenic potential will not be necessary.

### **Sponsor Response to Sub-questions 1 and 2**

*We acknowledge FDA's comments and CELLTRION would like to clarify the following:*

- a. *We are in agreement that there are inherent limitations in integrating all completed CT-P13 studies due to difference in design, patient population, dose level, concomitant medication use and region.*
- b. *Therefore to facilitate FDA review, our plan is to present all reported TEAEs, AEs leading to discontinuation and SAEs per individual study in 5.3.5.3, without integrating across studies and indications.*
- c. *For ESIs we are planning to present pooled analyses which will allow review by individual studies and across all studies and indications. Furthermore, it will be presented in the same table format as that submitted in the April 4<sup>th</sup> Submission package.*
- d. *Since electronic datasets for the Japanese study B1P13101 are not accessible, the safety data will be presented separately in its own CSR, without integrating with other studies.*

### **Sponsor Response to Sub-question 3**

*We acknowledge FDA response, part 3 on patients undergoing switch to CT-P13 and will duly address the recommendation by presenting a comparative table of safety and immunogenicity rates in the same patients, before and after the transition accompanied with discussion on limitations of this approach.*

### **Sponsor Response to Sub-question 4**

*We acknowledge your comments in regards to equivalence margins and we will follow your recommendation in justification of equivalence margins in 2.7.3.*

### **Sponsor Response to Sub-question 5**

*We acknowledge your comments on missing data and we will conduct DAS28 analysis in ITT patient population in CT-P13 3.1 study at week 30 in all randomized patients using sensitivity analyses to explore the impact of missing data imputation methods. Is that an acceptable approach?*

**Sponsor Response to Sub-question 6**

*No comment to this question*

**QUESTION 24**

CELLTRION plans to

(b) (4)

Does the FDA agree?

**FDA Response**

No, we do not agree. In our August 9, 2013 meeting minutes for the July 10, 2013 BPD Type 3 meeting held with you, we included a post-meeting note that provided further information about the required initial PSP. We stated, in part: "FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (PSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed PSP prior to the submission of your planned 351(k) BLA.... Sections 505B(e)(2)(C) and 505B(e)(3) set forth a process lasting up to 210 days for reaching agreement with FDA on an initial PSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the initial PSP... After the initial PSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by FDASIA. 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." The meeting discussion for question 19 at the July 10, 2013, meeting states: "Regarding timing of submission of the PSP, FDA advised Celltrion to submit their PSP as soon as possible based on Celltrion's assertion that they have completed their clinical development program except for the 3-way PK similarity study." We reiterate our recommendation to submit an initial PSP as soon as possible, and in advance of submission of your proposed BLA.

We also refer you to the draft Guidance for Industry entitled "*Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*" (July 2013), which explains that "[if] a phase 3 study, or a combined phase 2 and phase 3 study, will not be conducted, the sponsor should submit the initial PSP no later than 210 calendar days before a marketing application or supplement is submitted."

FDA cannot commit to spending less than 90 days to provide initial comments on your iPSP, or less than 30 days to confirm agreement with your agreed iPSP. However, it should be noted that you may opt to spend less than 90 days for review of our comments on your iPSP and submission of your agreed iPSP. You should submit an *agreed and confirmed* pediatric study plan with your BLA submission.

Your proposal to

(b) (4)

would not be appropriate for CT-P13. To address PREA, you

should consider, among other things, the indications for which US-licensed Remicade is licensed and where a justification for extrapolation across biological products (i.e., from the reference product to the proposed biosimilar product) could be provided in the context of your biosimilar development program. We note that Remicade has unexpired orphan exclusivity for pediatric ulcerative colitis; [REDACTED] (b) (4)

**Sponsor Response**

*We acknowledge your comment. We would like to report that we have submitted the iPSP on 25 April 2014.*

*The Sponsor would like to acknowledge the slight delay in submitting the PSP relative to BLA submission timeline. Our current plan is to submit the BLA in mid-July 2014. Based on this information, will this create any issue in terms of filing the BLA?*

**ADDITIONAL QUESTIONS**

- What is the total time from submission to decision (2+10=12 months or 10 months)
- Are FEI numbers required at time of submission or will a DUNS number be acceptable?

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PHUONG N TON  
06/04/2014



PIND 118135

**MEETING MINUTES**

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

Attention: Debra Hackett  
Senior Consultant

Dear Ms. Hackett:

Please refer to your Pre-Investigational New Drug Application (PIND) file for CT-P13.

We also refer to the meeting between representatives of your firm and the FDA on July 10, 2013. The purpose of the meeting was to discuss the development program for CT-P13, which is being developed as a proposed biosimilar product to US-licensed Remicade (infliximab).

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

If you have any questions, call me at (301) 796-796-1648.

Sincerely,

*{See appended electronic signature page}*

Nina Ton, Pharm.D.  
Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



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

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Biosimilar  
**Meeting Category:** BPD Type 3

**Meeting Date and Time:** July 10, 2013, 12:30 - 2:00 PM  
**Meeting Location:** White Oak Building 22, Conference Room 1315

**Application Number:** PIND 118135  
**Product Name:** CT-P13, a proposed biosimilar product to Remicade (infliximab)

**Indication:** Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis, Plaque Psoriasis, Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Pediatric Ulcerative Colitis

**Sponsor Name:** Celltrion, Inc.

**Meeting Chair:** Lydia Gilbert-McClain, M.D.  
**Meeting Recorder:** Nina Ton, Pharm.D.

**FDA ATTENDEES**

Lydia Gilbert-McClain, M.D., Deputy Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)  
Anthony G. Durmowicz, M.D., Clinical Team Leader, DPARP  
Stacy Chin, M.D. Clinical Reviewer, DPARP  
Janet Maynard, M.D., Clinical Reviewer, DPARP  
Nikolay Nikolov, M.D., Clinical Reviewer, DPARP  
Raj Nair, M.D., Clinical Reviewer, DPARP  
Matthew Whittaker, Ph.D., Pharmacology/Toxicology Reviewer, DPARP  
Nina Ton, Pharm.D., Regulatory Project Manager, DPARP  
Chandrasah Sahajwalla, Ph.D., Director, Division of Clinical Pharmacology II (DCP II), Office of Clinical Pharmacology (OCP)  
Satjit Brar, Ph.D., Pharm.D., B.S., Team Lead, DCP II, OCP  
Liang Zhao, Ph.D., Clinical Pharmacology Reviewer, DCP II, OCP  
Joan Buenconsejo, Ph.D., Biostatistics Team Leader, Division of Biometrics II, Office of Biostatistics (OB)  
Gregory Levin, Ph.D., Biostatistics Reviewer, Division of Biometrics II, OB  
Janice Weiner, J.D., M.P.H., Acting Director, Division of Regulatory Policy I, Office of Regulatory Policy  
David Frucht, M.D., Chief, Laboratory of Cell Biology, DMA, OBP  
George Miesegaes, Ph.D., Product Quality Reviewer, DMA, OBP

Kurt Brorson, Ph.D., Product Quality Reviewer, DMA, OBP  
Leah Christl, Ph.D., Associate Director for Therapeutic Biologics, Therapeutic Biologics and Biosimilars Team (TBBT)  
Sue Lim, M.D., Senior Staff Fellow, TBBT  
Carla Lankford, M.D., Ph.D., Science Policy Analyst, TBBT  
Neel Patel, Pharm.D., Regulatory Project Manager, TBBT  
Tyree Newman, Sr. Regulatory Health Project Manager, TBBT  
Gary Chiang, M.D., M.P.H., Medical Officer, Division of Dermatology and Dental Products  
David Kettl, M.D., Clinical Team Leader, Division of Dermatology and Dental Products

#### **FDA Attendees by Teleconference**

Timothy Robison, Ph.D., Pharmacology/Toxicology Team Leader, DPARP  
Farrokh Sohrabi, M.D., Medical Officer, Division of Gastroenterology and Inborn Errors Products

#### **SPONSOR ATTENDEES**

##### **Celltrion**

Shin Jae Chang, Ph.D., Vice President, R&D  
KiSung Kwon, Ph.D., Deputy Manager, Process II (R&D)  
SooYoung Lee, Ph.D., Director, Process I (R&D)  
HoUng Kim, Deputy Manager, Clinical Planning & Medical Affairs  
HyukJae Lee, Deputy Manager, Regulatory Affairs & Clinical Operations  
JaeHwee Park, Manager, Clinical Operation I  
MinKyoung Jeon, Ph.D., Assistant Manager, Corporate RA I  
HyeMi Cho, Assistant Manager, Corporate RA II  
Taek Sang Kwon, Staff, Clinical Planning

##### **Parexel**

Ravi Harapanhalli, Ph.D., Technical Vice President - CMC  
Keith Watson, Ph.D., Technical Vice President - CMC  
Cecil Nick, Ph.D., Technical Vice President - Clinical  
Partha Roy, Ph.D., Principal Consultant - Clinical  
(b)(4) Principal Consultant - Clinical  
Debra Hackett, Senior Consultant, Project Manager

##### **Celltrion Attendees by Teleconference**

HwangKeun Jun, Senior Manager, Non-Clinical Research & Biological Assay (R&D)  
SookMi Hwang, Senior Manager, Purification Process Manager, Corporate RA I  
ByoungOh Kwon, Manager, Purification Process  
DongSik Kim, Staff, Corporate RA II

##### **PAREXEL Attendee by Teleconference**

Sally Choe, Ph.D., Director

## 1. BACKGROUND

The purpose of the meeting is to discuss the development program for CT-P13, a proposed biosimilar to US-licensed Remicade. Celltrion submitted a meeting request dated March 18, 2013, to the Division of Pulmonary, Allergy, and Rheumatology Products, and the Division granted the meeting on April 8, 2013. The briefing package was submitted with the meeting request on March 18, 2013. The FDA provided preliminary comments to Celltrion on July 8, 2013. After the review of these comments, Debra Hackett, Parexel Senior Consultant, communicated to the Division via email dated July 9, 2013, that Celltrion has requested to focus the meeting discussion on CMC Questions 3, 5, 6, 8b, 11 and 12; Clinical Questions 15 through 18; and Regulatory Question 19. At the meeting on July 10, 2013, Celltrion provided handouts (attached in Section 7) that were presented during the introduction of the meeting. Celltrion's questions are in *italics*, the FDA's responses are in normal font, and the meeting discussion is in **bold**.

## 2. DISCUSSION

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

### CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

#### General comments

While the product quality data to support the initial IND filing to initiate clinical studies appear acceptable, more detailed information should be submitted with the IND submission. In particular, the manufacturing process should be described in greater detail than that provided in flow diagrams. In addition, primary data for stability testing and batch analysis should be provided, including representative chromatogram traces, SDS-PAGE gels, etc. We further recommend use of the eCTD format for the IND submission.

Our responses to your questions address the information that should be submitted with the initial IND. It is premature to discuss the acceptability of the information to support a BLA. These and related topics can be addressed during a BPD Type 4 meeting or other BPD meetings during the development of CT-P13.

#### Meeting Discussion

**Celltrion presented an overview of its planned timeline for the development and marketing of CT-P13 in the US as summarized in the attached slide presentation (slide 4).**

#### Question 1

*Does the Agency agree that the characterization and testing of the Master Cell Bank (MCB), Working Cell Bank (WCB), (b) (4) are sufficient to support clinical trials and BLA submission of the CT-P13 drug product?*

### **FDA Response**

While the overall plan for characterization and testing of the cell banks appears reasonable, additional details should be submitted to the forthcoming IND.

- a. Describe the assays used to detect bacteria/fungi, mycoplasma and viruses. Specify method(s) that incorporate(s) a PCR-based component.
- b. Include Certificates of Analysis (CoAs) for all animal-derived raw materials (e.g., (b) (4)). Ensure that the CoAs contain documentation of the country of origin, commercial source, and raw material testing requirements.
- c. Provide data that support and clarify statements made on page 57 of the meeting package (i.e., that minor differences in oligosaccharide profiles (Table 7) are “caused (b) (4) ... rather than a trend and/or assay variability”). For example, address whether an N-linked glycan comparison of samples produced under the same process conditions addresses this issue. Alternatively, the data that support the statement made on page 58 of the meeting package, (b) (4), should be provided.
- d. Detailed information on the procedures used to generate and clone the new cell line should be submitted to the IND. The supportive information also should include a description of the expression plasmid (including DNA sequence and parental cell lines, if applicable), transfection protocol, cloning procedure and composition of the expansion and production media.
- e. (b) (4)

### **Meeting Discussion**

Celltrion acknowledged the FDA response and agreed to provide the requested data. This question was not discussed.

### **Question 2**

*Does the Agency agree that the viral clearance study results for the (b) (4) is sufficient to support clinical trials and BLA submission of the CT-P13 drug product?*

### **FDA Response**

While the overall viral safety assurance plan appears adequate, additional details should be included in the IND. Describe the small scale models used in process validation for viral clearance. Note that the small scale process models should be representative of manufacturing

scale, especially with regard to matching critical process parameters. A line-by-line list of critical process parameters for each viral clearance unit operation matched between large scale and small scale should be included in a tabular format in the IND submission.

### **Meeting Discussion**

**Celltrion acknowledged the FDA response and agreed to provide the requested data. This question was not discussed.**

### **Question 3**

*Does the Agency agree that the Sp2/0 HCP ELISA method which utilizes an antibody raised against host cell proteins derived from a Sp2/0-Ag14 cell line is a suitable method to monitor host cell protein contamination during (b) (4) testing of CT-P13 drug substance?*

### **FDA Response**

An assessment cannot be made regarding the acceptability of the ELISA-based host cell protein assay, as only a brief summary information was submitted with the meeting package. Provide a summary description of both assays and the source (in-house or commercial) of the antisera used for detection of host cell protein impurities (HCPs).

The proposed ELISA-based method should be demonstrated to possess adequate HCP coverage and should be as sensitive as the original method described on page 64. It is unclear whether the data presented in Figure 7 and Tables 12-13 support the claim that the assays were qualified or that they possess similar performance characteristics. In the IND, include details of the assay qualification and comparability assessment methods that were used to generate the data shown in Tables 12 and 13.

The anti-HCP antiserum used in the ELISA-based method needs to be qualified for its ability to detect potential HCP impurities. This assessment should include 2D SDS-PAGE gels of the range of HCPs detected by a sensitive protein stain, such as silver stain, compared to the range detected by western blot analysis using the antiserum employed in the assay. It is possible to use a similarly sensitive and discriminating assay in lieu of the 2D SDS-PAGE assay. If an alternative approach is pursued, consultation with the Agency is recommended. These data should be used to determine the approximate percent of potential HCP impurities that are recognized by the HCP antiserum. Analysis of HCP coverage by a 1-dimensional SDS-PAGE gel method is not sufficiently informative for this purpose.

Clarify whether the ELISA assays being used to detect host cell protein (HCP) impurities are non-Celltrion commercial kits. Commercial kits are usually insensitive at detecting product-specific HCPs. If you use a commercial kit(s), provide data demonstrating that the commercial kit(s) can detect the majority of proteins present in your Sp2/0-Ag14 cell extract.

### **Meeting Discussion**

**Celltrion stated that assay description(s) could be provided in the original IND submission, but the additional analysis of the anti-sera specificity described above would require some time to complete and would need to be submitted in a follow-up amendment. The FDA responded that it would be acceptable to submit this information to the IND when it is**

**available and that this would not be a hold issue for initiating the proposed clinical study under the IND. The FDA advised Celltrion that a 2D gel would be a sensitive manner to evaluate the antisera specificity range for potential HCP impurities.**

**Question 4**

*Does the Agency agree that the proposed CT-P13 drug substance release specifications are sufficient to support clinical trials and BLA submission of the CT-P13 drug product?*

**FDA Response**

While the release tests and specifications shown in Table 14 appear reasonable, additional information should be submitted with the IND submission. Adequacy of the data is a review issue. Provide a detailed description of each test method as well as their corresponding qualification/ validation procedures and a justification of the acceptance criteria with the IND.

**Meeting Discussion**

**Refer to Discussion under Question 5.**

**Question 5**

*Does the Agency agree that the specification proposed for release testing of the CT-P13 drug product, is sufficient to support clinical trials and BLA submission of the CT-P13 drug product?*

**FDA Response**

See response to Question 4. We also recommend that in addition to USP <788> particulate testing, sub-visible particles <10 µm in size be characterized at release and at regular intervals in the drug product stability program under accelerated and/or stressed condition.

**Meeting Discussion**

**Celltrion agreed to provide a detailed description of each test method as well as their corresponding qualification/validation procedure for drug substance release. Regarding particulate testing, Celltrion proposed** (b) (4)

**The FDA stated that this scheme does not provide an adequate picture of the kinetics of particle accumulation. Instead, the Agency advised Celltrion to evaluate particulates at time 0, month 3, month 6, year 1, year 2, and year 3. Celltrion commented that it has completed most of these studies of the primary batches for the EMA Marketing Authorization Application (MAA); thus, Celltrion has data for the existing samples at month zero and month 36. However, going forward for new drug product batches, Celltrion will implement the FDA's recommendation and provide particulate testing at all the additional recommended time points. FDA noted that the data should be provided to the IND as it becomes available.**

**Question 6**

*Does the Agency agree that the proposed bioassay is adequate for controlling drug substance and drug product bioactivity to support clinical trials and BLA submission of the CT-P13 drug product?*

**FDA Response**

Although inclusion of a TNF $\alpha$  neutralization assay and the use of a WEHI164 mouse sarcoma cell line are appropriate, the proposed bioassay might not assess the entire scope of the *in vivo* mechanism(s) of action for CT-P13, including potential Fc effector function. For this reason, justify the assay's relevance to Fc $\gamma$ RIIIa binding activity. If this assay does not measure this product attribute, development of a specific assay for the Fc effector function should be considered.

### **Meeting Discussion**

**Celltrion proposed to perform glycoform analysis in order to evaluate Fc function instead of measuring binding activity. Celltrion justified this proposal by stating that Fc effector function is controlled by glycans, and that the glycan profiling is a very precise assay. The FDA responded that glycoform analysis would be an indirect measurement, and advised Celltrion to implement their established Biacore assay for the purpose of glycoform analysis for release testing. Celltrion expressed concern with chip-to-chip variation as the chips are washed and re-used. The FDA advised that Celltrion could control chip and run-to-run variation by including a reference standard in the assay. Celltrion stated that they would take the FDA's recommendations under advisement, but did not commit to conducting the recommended testing. The FDA stated that Celltrion could present their argument of not to conduct the recommended testing in terms of risk-assessment and by justifying the chosen testing approach. This information should be submitted to the IND for FDA review and comment.**

### **Question 7**

*Does the Agency agree that the proposed stability testing program is adequate to support clinical trials and BLA submission of the CT-P13 drug product?*

### **FDA Response**

While the overall proposed testing program is generally acceptable, further clarification is warranted. Specifications for the stability tests performed, currently described as "that for release testing with minor modifications", should be justified and further explained in a narrative. Actual data from test articles at each time point should be submitted in the IND, in a tabular format.

### **Meeting Discussion**

**Celltrion commented that all requested data will be provided. Celltrion stated that comparative stability testing between US-licensed Remicade and CT-P13 would not be meaningful, as the manufacture date, and therefore age, of US-licensed Remicade lots tested would be unknown. Furthermore, Celltrion stated that a forced degradation study was conducted for the EMA MAA submission. The FDA noted that real-time stability data is not intended to be part of the similarity assessment. With respect to the forced degradation and accelerated stability studies, the FDA stated that these studies are a part of the analytical similarity assessment and should be conducted in comparison with the US-licensed reference product. The FDA noted that if Celltrion did not plan to perform these studies, a justification, including risk assessment, for their proposed approach should be submitted to the IND.**

**Question 8**

*Does the Agency agree that the comparability study design and data are sufficient to demonstrate comparability of CT-P13 drug substance batches produced for nonclinical and clinical studies using Process A and Process B?*

**FDA Response**

The overall comparability program appears reasonable, but a determination regarding comparability will be a review issue. Refer also to the FDA Response to Questions 4-5 regarding assay selection and qualification/validation. We have the following additional comments regarding the comparability data to be submitted in the IND:

- a. Clarify whether Process B is currently intended to be representative of the final commercial process, or whether you anticipate additional major changes to manufacturing over time.
- b. Describe how comparability acceptance criteria were developed and justified. Address whether they were based on statistical considerations.
- c. Representative primary comparability study data from key tests should be submitted. These data should include CD- spectra traces, DSC traces, HPLC chromatograms, SPR traces, SDS-PAGE gels, and any other data of relevance to the overall comparability study assessment.

**Meeting Discussion**

**Celltrion clarified that the change from Process A to B was made early in development, and that all critical data (nonclinical, clinical) came from use of Process B material.** (b) (4)

**With respect to FDA comment b, the FDA clarified that they were asking that Celltrion provide clarification on what was done, and were not requesting additional testing to be performed at this time. Celltrion should submit this information to the IND.**

**With respect to FDA comment c, the FDA clarified that the raw data should be provided in the IND.**

**Question 9**

*Does the Agency agree that the comparability study design and data are sufficient to demonstrate comparability of CT P13 drug product batches produced for nonclinical and clinical studies at BINEX and Rentschler Biotechnologie, respectively?*

**FDA Response**

See FDA Response to Question 8.

**Meeting Discussion**

**This question was not discussed.**

**Question 10**

*Does the Agency agree that the proposed comparability study design and data is sufficient to demonstrate comparability of CT P13 drug product batches produced at Rentschler Biotechnologie and CELLTRION Plant (b) (4)?*

**FDA Response**

See FDA Response to Question 8.

**Meeting Discussion**

**This question was not discussed.**

**“Questions on Biosimilarity of CT-P13 versus US and EU Remicade”**

**General Comments**

As a preliminary matter, biosimilarity means that the proposed biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product (section 351(i) of the PHS Act). In addition, the BPCI Act defines the “reference product” for a proposed biosimilar biological product to mean the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) application (see section 351(i)(4) of the PHS Act). Under this statutory provision, US-licensed product Remicade (infliximab) would be considered the reference product. Accordingly, FDA’s use of the term “reference product” throughout these responses refers to US-licensed Remicade.

At this time, it is premature to make a determination that CT-P13 is highly similar to the reference product. The determination of analytical similarity will be a review issue.

Justify the intended number of clinical or to-be-marketed lots of CT-P13 drug substance and/or drug product as well as the number of US-licensed Remicade and EU-approved infliximab lots that will be used in the analytical similarity exercise.

**Question 11**

*Based on the quality data provided, does the FDA concur that the 2-way analytical similarity assessment has adequately demonstrated similarity of CT P13 to Remicade® sourced from EU and that with the bridge established by the 3-way similarity assessment of the analytical data with US-licensed Remicade®, CT P13 qualifies for a biosimilar program versus US-sourced Remicade® under section 351(k) of the Public Health Service Act (PHS)?*

**FDA Response**

Based on the data and information provided to date, FDA does not concur that the 2-way analytical similarity assessment is adequate. While the CT-P13 product has demonstrated similarity to EU-approved infliximab in a variety of assays, disparate results were noted in two assays:

- CE-SDS, where CT-P13 displayed 3-4% lower levels of intact antibody, commensurate with increased levels of H2:L1 species.
- SPR of FcγRIIIa binding, where CT-P13 displayed approximately 23% lower binding affinity.

We note that a substantial assessment and justification was provided to address these analytical differences and their potential impact *in vivo*. The data you provided from the PBMC ADCC activity assay were supportive of similar Fc effector function between the two products. We also note that you employed an additional ADCC activity assay with NK cells (Table 68), which did not appear to show differences within the variability of the assay. Describe the NK enrichment procedure and if these cells are predicted to be sensitive to FcγRIIIa binding changes or if other FcγR's could mediate redundant signal transduction with these two cell types. Provide a complete description of the procedures for both the PBMC and NK ADCC assays, including their qualification.

### Meeting Discussion

**Celltrion noted that in the 2-way analytical similarity assessment, the presence of 3-4% higher levels of H2:L1 variants was consistent in all CT-P13 batches compared to EU-approved infliximab. Celltrion acknowledged the difference and stated that their intended course of action is to investigate this finding and, if appropriate, optimizing the manufacturing process to lower the levels of this variant if it could be accomplished without impacting other quality attributes.**

**Celltrion attributed the observed differences in FcγRIIIa binding between CT-P13 and EU-approved infliximab to an intrinsic product-related substance, not an impurity. Celltrion asked what additional justification would be needed to demonstrate that the binding difference would not preclude a conclusion of biosimilarity. The FDA responded that, based on the information provided in the briefing package, the Agency could not make a determination that CT-P13 and US-licensed Remicade were highly similar. The FDA asked Celltrion to justify the use of the assays and to provide a more detailed description of the ADCC assays presented in the meeting package (i.e both PBMC and NK-cell based). Nevertheless, the FDA agreed with Celltrion that NK cells are the preferred cell type for assessing ADCC activity.**

**In summary, Celltrion should provide a robust data package to support that CT-P13 is highly similar to US-licensed Remicade, including the requested additional information on the ADCC assays. Celltrion should justify the conclusion that the observed 23% difference in binding does not have clinical impact. While this is not a requirement to initiate the planned clinical studies, this data should be submitted as early as possible.**

**The FDA reiterated that EU-approved infliximab is not a “reference product”; the FDA stated that only US-licensed Remicade would be considered as the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) application.**

**Celltrion questioned the importance of ADCC in different disease areas, in particular rheumatologic indications. The FDA recommended that a panel of functional quality attributes, including ADCC, should be evaluated as part of the three-way similarity exercise. Celltrion responded that the majority of the assays used to compare CT-P13 with EU-approved infliximab found no functional or biochemical difference between the products. However, Celltrion stated that they understood the FDA’s request to provide the results of robust analytical testing between CT-P13 and US-licensed Remicade.**

**Question 12**

*Based on the quality data provided, does the FDA concur that the abridged 3-way similarity assessment has adequately demonstrated similarity of CT-P13 versus Remicade® sourced from US and EU and therefore a bridge has been established with the detailed 2-way similarity assessment conducted between EU-sourced Remicade® and CT-P13?*

**FDA Response**

FDA does not concur that the data provided to date from the “abridged 3-way similarity assessment” (assessment of CT-P13 to US-licensed Remicade and EU-approved infliximab) is adequate, nor does FDA concur that a bridge has been established with the 2-way similarity assessment.

Under the BPCI Act, a biological product may be demonstrated to be “biosimilar” if data show that, among other things, the product is “highly similar” to an FDA-licensed biological product. As a scientific matter, robust and complete analytical similarity data directly comparing CT-P13 with the reference product, US-licensed Remicade, is needed. Your “abridged 3-way similarity assessment” -- as a bridge to the more robust 2-way analytical similarity data between your proposed biosimilar product and non-US-licensed comparator product – is not acceptable. Furthermore, analytical differences have been noted between CT-P13 and EU-approved infliximab (Question 11), which have not been adequately addressed. The lack of adequate data and information to address the noted differences coupled with the lack of adequate data comparing CT-P13 and US-licensed Remicade raise uncertainty at this point in time about the analytical similarity of CT-P13 to US-licensed Remicade.

Address the following in the forthcoming IND:

1. Provide adequate information to support a demonstration of biosimilarity based on data directly comparing the proposed product with the reference product (US-licensed Remicade).
2. Given that FcγR binding differences were observed between CT-P13 and EU-approved infliximab (see Question 11), ensure that you adequately assess these attributes in the 3-way similarity assessment. A full complement of Fc receptor and antigen binding assays (i.e. the SPR analytical methods used in the two-way analysis) should be included in the 3-way similarity analysis. A complete description of the SPR assays should be provided, including how FcR reagents were sourced and prepared and how the assays were qualified. The description should include a discussion of how the chips were

washed/regenerated between test articles and whether CT-P13, US-licensed Remicade and EU-approved infliximab were run on the same day with the same chip.

3. We noted that three batches of each product were studied for the 3-way similarity assessment. You will need to justify the intended number of clinical or to-be-marketed lots of CT-P13 drug substance and/or drug product as well as the number of US-licensed Remicade and EU-approved infliximab lots that will be used in the analytical similarity exercise. Reference product lots should be selected across the shelf-life of the product. You should also justify the selection of the reference product lot(s) used in the analytical studies as being representative of the reference product, and appropriately within the expected range of variability of the reference product.
4. The NK cell ADCC assay should be included in the three-way analytical similarity assessment with the full complements of lots that will be tested in other assays.

From a product quality perspective, a determination of structural and functional similarity should be supported through a statistical analysis of data from multiple lots. Whether the number of lots chosen for this analysis can produce data of adequate statistical power will be a review issue.

### **Meeting Discussion**

**Celltrion agreed to conduct the 3-way “enhanced” similarity assessment as recommended by the FDA. Celltrion asked whether using 3 lots of each product (i.e., CT-P13, US-licensed Remicade, and EU-approved infliximab) in the assessment would be sufficient. The FDA responded that the Agency cannot specify an exact number of lots needed for a meaningful statistical evaluation of similarity, as this would depend on a number of factors, such as lot-to-lot variability. The FDA added that as many lots as feasible should be compared, including all Celltrion batches produced to date, and that the number of lots tested and the statistical analysis should be adequately justified.**

**The FDA indicated that the data obtained so far and presented in the package (3 lots of each product) would be acceptable for an initial IND submission. However, the analysis of 3 lots of each product would unlikely be sufficient for demonstrating analytical similarity to support a 351(k) BLA. Celltrion proposed that they could feasibly compare 6 to 10 lots of each product and submit this data as an amendment after the initial IND submission. The FDA stated that acceptability of the 6 to 10 lot data to support a demonstration of analytical similarity will be a review issue.**

### **NONCLINICAL**

#### **Question 13**

*Based on the extensive and comprehensive quality, nonclinical and clinical similarity assessments between CT-P13 and the EU sourced Remicade®, and the proposed 3-way EU/US/CT-P13 quality and clinical PK bridge, does the Division agree that no additional nonclinical studies are required to support an IND and the subsequent biosimilar BLA?*

### **FDA Response**

The value of safety and exposure data collected from toxicity studies in the rat, a non-relevant species, to support clinical trials with CT-P13 is questionable. An *in vivo* study in mice expressing human TNF $\alpha$  (e.g. Tg197 mice) to assess the safety and similarity of CT-P13 relative to US-licensed Remicade would have been more informative. However, pending review of clinical data from your studies already conducted in patients with RA and AS, we agree that no additional animal studies are required to support opening an IND and initiating clinical studies.

Whether further animal studies will be required to support the planned BLA remains a review issue. However, if after review of data, we conclude that the similarity assessment of CT-P13 to US-licensed Remicade is adequate from a nonclinical perspective, then the reproductive toxicology, immunotoxicity, safety pharmacology and an evaluation of the carcinogenic potential (e.g., review of nonclinical studies and published scientific literature for any tissue proliferative or immunosuppressive effects associated with infliximab) will not be needed.

### **Meeting Discussion**

**This question was not discussed.**

## **CLINICAL**

### **Question 14**

*Clinical studies have been conducted demonstrating similarity of CT-P13 to Remicade® that was sourced from Europe. CELLTRION is planning to run a 3-way healthy volunteer PK study using US licensed Remicade®, EU sourced Remicade®, and CT-P13 to evaluate the similarity of the products and to bridge to clinical data from the studies conducted to support the MAA in Europe. The design for the proposed clinical study is included in the Briefing Package.*

*Does the FDA agree with this proposal?*

### **FDA Response**

We agree with your proposed plan to conduct a single-dose parallel PK study in healthy volunteers. In addition to AUC<sub>inf</sub> and C<sub>max</sub>, we recommend that you also include AUC<sub>last</sub> in the PK similarity assessment. Pharmacokinetic similarity should be evaluated for all three PK variables using the pre-specified acceptance criteria for all three pair-wise comparisons (CT-P13 vs. EU-approved infliximab, CT-P13 vs. US-licensed Remicade, and EU-approved infliximab vs. US-licensed Remicade). In addition, in the absence of a valid justification, we suggest that you include both male and female subjects in the proposed study.

### **Meeting Discussion**

**Celltrion stated that they would include the FDA recommended additional PK parameters in the analysis and will evaluate PK similarity for all three pair-wise comparisons (US-licensed Remicade vs. EU-approved infliximab, CT-P13 vs. EU-approved infliximab, and CT-P13 vs. US-licensed Remicade). Celltrion asked for confirmation as to whether the 3-way PK similarity study, with the recommended changes, would be sufficient to provide an adequate bridge to data from their completed clinical studies. The FDA stated that while the adequacy of the data would be a review issue, Celltrion's proposed PK similarity study,**

**with the recommended changes, in addition to adequate analytical similarity data, would be a reasonable approach to establish a scientific bridge to the US-licensed reference product and to the existing clinical data obtained using EU-approved infliximab. Celltrion asked whether the conduct of the PK similarity study in Germany would pose any issues. The FDA responded that there is no issue conducting the study in Germany if the study is conducted with the proposed protocol.**

### **Question 15**

*CELLTRION has developed and validated an assay to detect the presence of antibodies to drug product and whether anti-drug antibodies possess neutralizing activity. The assays were used to analyze samples from both CT-P13 and the reference drug Remicade® (EU sourced) treated patients. Results showed a similar level of antibody formation in the two patient populations, in line with what has been reported for the incidence of antibodies to Remicade®. Data will be presented on the assay methods, testing approach, results of testing, and a comparative evaluation of immunogenicity response between CT-P13 and Remicade®.*

*Does the Division agree that these data support the biosimilarity of CT-P13 to Remicade®?*

### **FDA Response**

Provide a detailed description of the methodology and plans for validation of the assays that will be used for the detection of ADA in the IND submission. The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to product interference. The validated assays should be capable of sensitively detecting ADA responses to the proposed biosimilar, US-licensed Remicade, and EU-approved infliximab in the presence of drug levels that are expected to be present at the time of patient sampling. Information on the expected product levels that will be present in patient samples should be included to support use of the assay. An assay should also be developed that is able to delineate neutralizing ADA responses.

We refer you to the Draft Guidance for Industry, “*Assay Development for Immunogenicity Testing of Therapeutic Proteins*” for important aspects of immunogenicity assay development. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750.pdf>

The determination of a similar level of antibody formation/immunogenicity between your CT-P13 product and EU-approved infliximab will be a review issue. However, while a similar incidence of antibody formation between patients receiving CT-P13 and EU-approved infliximab is reassuring, the use of this immunogenicity data to support biosimilarity to the reference product is limited.

### **Meeting Discussion**

**Celltrion has developed and used an assay for the detection of ADA to both CT-P13 and EU-approved infliximab. For this assay, EU-approved infliximab was used as the reference standard. Celltrion inquired if this same assay could be used to analyze results from the proposed 3-way PK similarity study, and also whether US-licensed Remicade had to be used as the reference standard. The FDA responded that the assay could be used if Celltrion could provide justification that the assay was sensitive to the detection of ADA**

**responses to all 3 products. The FDA added that the standard sandwich ELISA may have limitations due to product interference, and, regardless of the assay selected, it should be sensitive to all immunoglobulin isotypes, although differentiation (isotyping) is not expected. Regarding the reference standard, the FDA recommended the use of US-licensed Remicade; however, if Celltrion chose to use EU-approved infliximab as the reference standard instead, they should provide justification that the use of this reference standard did not produce any differential effect.**

**Question 16**

*CELLTRION believes that data package described herein along with the scientific justification for extrapolation laid out in the briefing package meet the proposed requirement for extrapolation to the other approved indications for Remicade®.*

*Does the FDA agree?*

**FDA Response**

If CT-P13 meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, the potential exists for CT-P13 to be licensed for one or more additional conditions of use for which the reference product is licensed. You would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which you seek licensure.

Such scientific justification for extrapolation should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action in each condition of use which licensure is sought; this may include:
  - The target/receptor(s) for each relevant activity/function of the product;
  - The binding, dose/concentration response and pattern of molecular signaling upon engagement of target/receptors;
  - The relationships between product structure and target/receptor interactions;
  - The location and expression of the target/receptor(s)
- The pharmacokinetics and biodistribution of the product in different patient populations; relevant PD measures also may provide important information on the mechanism of action.
- Differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to “off-target” activities).
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population from which licensure is sought.

Specific to your CT-P13 development program, as noted in the FDA Response to Question 11, differences in FcγRIII binding and its potential effect on ADCC activity lead to residual uncertainty regarding the biosimilarity of CT-P13 to the US-licensed reference product, Remicade. We encourage you to investigate and, if appropriate, incorporate changes to your manufacturing process that would result in a CT-P13 product that better matches the critical quality attributes of US-licensed Remicade. Persistent differences in critical quality attributes which are verified may significantly impact your ability to demonstrate that CT-P13 is highly similar to US-licensed Remicade and to extrapolate to other indications.

Based on the apparent differences between your current product and US-licensed Remicade, you will need to address residual uncertainty created by differences in Fc effector function in the conditions of use for which you seek licensure for CT-P13. If you can justify based on analytical, animal, PK and PD, and other data or information that only minimal residual uncertainty exists, then the general design features of your completed clinical study in patients with RA could be used to (1) support a demonstration of no clinically meaningful differences between CT-P13 and US-licensed Remicade, with data from a single transition, as discussed in the response to Question 17, and (2) support extrapolation to other approved conditions of use for US-licensed Remicade.

We also remind you that a proposed biosimilar product may only seek licensure for condition(s) of use that have been previously approved for the reference product (see section 351(k)(2)(A)(i)(III) of the PHS Act).

### **Meeting Discussion**

**Celltrion asked the FDA to clarify the comment regarding changes to the manufacturing process. The FDA responded that Celltrion must address residual uncertainty regarding the similarity of CT-P13 to US-licensed Remicade. This would involve investigating the differences and, in some cases if necessary, changing the manufacturing process to result in a CT-P13 product that better matches the critical quality attributes of the reference product (US-licensed Remicade). In other cases, or in addition to changing the manufacturing process, Celltrion may provide additional analytical, animal, PK, or PD data to justify that only minimal uncertainty exists. The FDA cautioned that changes to the manufacturing process to optimize one quality attribute risks introducing changes to other quality attributes and should be undertaken with caution.**

### **Question 17**

*During clinical development, approximately 400 patients have been exposed to CT-P13 for 1 year. Does the FDA consider these premarketing safety and immunogenicity data sufficient for submission of an application for CT-P13 seeking marketing authorization as a biosimilar to Remicade®?*

### **FDA Response**

You should assess safety and immunogenicity in the setting of patients who undergo a single transition from US-licensed Remicade to CT-P13 to provide a descriptive comparison with patients who continue on US-licensed Remicade.

While the size of the proposed safety database may be sufficient, the acceptability of the safety database in the absence of data from a single transition will be a review issue.

If you conduct a separate study to obtain safety and immunogenicity data from a single transition, we recommend that you pre-specify windows of attribution for adverse events regarding the specific study drug, as well as prespecified events of special interest, including anaphylaxis and hypersensitivity reactions. When classifying these types of events, we recommend that you use the definitions by Sampson et al (Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary Report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006; 117(2):391-97). This information should be submitted with the BLA.

### **Meeting discussion**

**Celltrion questioned the need to collect the requested transition data, but stated that they understood the FDA's concerns with immunogenicity, infusion-related issues, and other adverse drug reactions. Celltrion stated they have collected safety data from over 700 patients who have received CT-P13, including patients who have undergone a single transition from EU-approved infliximab to CT-P13. Celltrion asked if their existing safety database for CT-P13 along with the large body of pre- and post-marketing safety data on EU-approved infliximab and US-licensed Remicade would be sufficient to address uncertainty about safety and immunogenicity. Celltrion stated they were not certain any additional relevant information could be obtained in the pre-market setting, and proposed a post-market safety assessment. The FDA responded that the rationale for obtaining transition data from US-licensed Remicade to CT-P13 was to evaluate a real-world scenario of when the proposed biosimilar would enter the marketplace and non-treatment naïve patients may undergo a single transition to CT-P13. The study would not need to be powered to detect differences, but would provide a descriptive analysis of the acute adverse events (e.g., hypersensitivity) that may occur in the immediate period following a transition in a non-treatment naïve population.**

**Ideally, the FDA would like Celltrion to assess the risk of patients switching from US-licensed Remicade to CT-P13 and to compare those patients to patients who continue on US-licensed Remicade. Whether or not the single transition data from EU-approved infliximab to CT-P13 would be sufficient will be a review issue. Celltrion stated they have not analyzed the transition data that they have collected, but plan to submit the data for feedback after opening the IND. The FDA stated that this approach was acceptable, but recommended submitting the transition data well in advance of the submission of the BLA.**

### **Question 18**

*The pivotal Phase 3 trial in conducted to support the MAA demonstrated the similarity of CT-P13 and EU sourced Remicade® for the treatment of patients with Rheumatoid Arthritis. In addition, CELLTRION had completed two supportive clinical studies: one PK/efficacy study in Ankylosing spondylitis patients and one small pilot study in RA patients.*

*Does the FDA agree that data from these studies using European reference product along with the data from the proposed healthy volunteer PK study and other supporting data described in the Briefing Package would be supportive of a biosimilar marketing application of CT-P13 in the US?*

### **FDA Response**

We do not agree that the data you have proposed in your briefing package would be adequate to support a biosimilar marketing application for CT-P13 in the US.

If you seek to use data from clinical studies comparing CT-P13 to EU-approved infliximab to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, you should provide adequate data or information to scientifically justify the relevance of this comparative data to an assessment of biosimilarity and establish an acceptable scientific bridge to the US-licensed reference product. The type of bridging data needed to provide adequate scientific justification for this approach would likely include a bridging clinical PK and/or PD study, as well as a direct physicochemical comparison of all 3 products: US-licensed Remicade to CT-P13, EU-approved infliximab to CT-P13, and EU-approved infliximab to US-licensed Remicade. All three comparisons should meet the pre-specified acceptance criteria for analytical and PK and/or PD similarity. The adequacy of this scientific justification and bridge to the US-licensed reference product would be a review issue.

Therefore while you have proposed to conduct a 3-arm PK similarity study in healthy volunteers, you will need an adequate analytical similarity exercise, that is more robust than you have proposed, comparing all 3 products to establish an adequate scientific bridge to the US-licensed reference product (see response to Question 12). Also, as noted in our response to Question 16, there are differences between CT-P13 and EU-approved infliximab that raise residual uncertainty regarding whether CT-P13 is biosimilar to US-licensed Remicade. You will need to address these differences, as described. See also the response to Question 17, regarding a single transition from US-licensed Remicade to CT-P13.

Lastly, regional differences in clinical practice may affect the applicability of the study results obtained from sites outside the US to the US population. You will need to demonstrate that the results from your comparative clinical study can be extrapolated to the US population.

### **Meeting Discussion**

**To address the FDA's comment regarding the regional differences in clinical practice, Celltrion noted that the study design of their clinical trials mirror the study designs of the clinical trials which supported approval of US-licensed Remicade. Celltrion explained that the aim of their clinical development program was to use RA and AS patients as "model populations" to evaluate differences, and from these data extrapolate to other indications. Celltrion further stated that the dose and background therapy were identical to those used in the US, and that their results were relevant to the US population. The FDA reiterated that establishing a bridge between EU-approved infliximab and US-licensed Remicade would be critical to Celltrion's ability to justify the relevance of data from clinical studies already completed with EU-approved infliximab as the comparator to support a demonstration of biosimilarity to US-licensed Remicade.**

## REGULATORY

### Question 19

*CELLTRION plans to submit*

(b) (4)

### FDA Response

Under the Pediatric Research Equity Act [section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355c)], all applications for new active ingredients, 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 (n) 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 or deferred.

### Meeting Discussion

**Celltrion stated they understood the PREA requirements for pediatric assessment and the justification needed to extrapolate to pediatric indications. However, Celltrion asked for clarification regarding obtaining pediatric indications and interchangeability, as a product that is interchangeable with a reference product is not considered to have a "new active ingredient" and thus does not trigger PREA. The FDA responded that Celltrion would need to address PREA for its proposed biosimilar product and submit a pediatric study plan (PSP) unless the requirement is waived or deferred. A PSP could potentially consist of a justification for extrapolation of use to the pediatric population based on, among other things, the factors listed in the response to Question 16. Additional clinical trials in the pediatric population may not be needed. Regarding timing of submission of the PSP, FDA advised Celltrion to submit their PSP as soon as possible based on Celltrion's assertion that they have completed their clinical development program except for the 3-way PK similarity study. The FDA added that the Agency has not made public statements regarding interchangeability and that FDA did not have further comments at this time. If Celltrion was interested in pursuing a demonstration of interchangeability, the FDA encouraged Celltrion to submit a specific proposal for FDA comment in the context of a specific development program.**

### Question 20

*Based on the current and proposed quality, nonclinical and clinical similarity assessments between CT-P13 and the EU sourced Remicade®, and the proposed 3-way EU/US/CT-P13 quality and clinical PK bridge, does the Division agree that this program will adequately support an IND and the subsequent biosimilar BLA?*

### **FDA Response**

Whether the current and proposed assessments will adequately support an IND and the subsequent BLA will be a review issue. Refer to the FDA Responses to your other questions regarding the data and information necessary to support an IND and BLA.

### **Meeting Discussion**

**This question was not discussed.**

### **Question 21**

*Dependent on the outcome of this Type 2 meeting, CELLTRION plans to request a BPD Type 4 meeting for the next discussion of the program and the plans for the BLA. Does the FDA concur?*

### **FDA Response**

At an appropriate time prior to submitting your BLA, we encourage you to request a BPD Type 4 meeting request to discuss the format and content of your BLA.

### **Meeting Discussion**

**This question was not discussed.**

### **Post-Meeting Note**

**Celltrion sent an email dated July 18, 2013, to clarify whether the FcγRIIIa and/or ADCC assay data using US-licensed Remicade could be submitted following the submission of the initial IND, or if it was needed at the time of initial IND submission. The FDA responded via email dated July 25, 2013, that FcγRIIIa and/or ADCC assay data using US-licensed Remicade could be submitted following the submission of the initial IND, but it was strongly recommended to perform these studies as early thereafter, and submit the results as soon as available.**

## **3. PREA PEDIATRIC STUDY PLAN**

Under the Pediatric Research Equity Act [section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21U.S.C. 355c)], all applications for new active ingredients, 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(n) 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 or deferred. We encourage you to submit plans for pediatric studies during the IND stage of drug development.

### **Post-Meeting Note**

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

**submission of your planned 351(k) BLA; see additional comments below regarding expected review timelines.**

**Section 506 of the Food and Drug Administration Safety and Innovation Act (FDASIA) amended section 505B(e) of the FD&C Act to set forth a process for reaching agreement between applicants and FDA on initial PSPs. This provision of FDASIA has an effective date of January 5, 2013. Section 505B(e)(2)(A) of the FD&C Act as amended by FDASIA provides that applicants should submit an initial PSP no later than 60 calendar days after the date of the end-of-Phase 2 meeting, or at another time agreed upon by FDA and the applicant. As required by FDASIA, FDA has issued guidance on PSP requirements, including timing of PSP submission. Refer to **Guidance for Industry Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans** at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>**

**Sections 505B(e)(2)(C) and 505B(e)(3) set forth a process lasting up to 210 days for reaching agreement with FDA on an initial PSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the initial PSP. The initial PSP must include an outline of the pediatric study or studies that a sponsor plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. After the initial PSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by FDASIA. 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.**

#### **4. DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation 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 studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of 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. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

#### **5. ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion

#### **6. ACTION ITEMS**

There were no action items.

## **7. HANDOUTS**

The handouts presented by Celltrion during the July 10, 2013 meeting are attached.

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PHUONG N TON  
08/09/2013