

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125289**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**PEDIATRIC PAGE**

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125289

Supplement Number: \_\_\_\_\_

NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: DAARP

PDUFA Goal Date: 4/24/09

Stamp Date: 6/24/08

Proprietary Name: SIMPONI

Established/Generic Name: Golimumab

Dosage Form: For all three indications, 50 mg given subcutaneously once monthly (supplied as a solution in a prefilled syringe and autoinjector)

Applicant/Sponsor: Centocor

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): 3  
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Rheumatoid Arthritis

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

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

Does the division agree that this is a complete response to the PMC/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*	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	0 yr. __ mo.	<2 yr. __ mo.	<input checked="" 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 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	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 checked="" type="checkbox"/> Other	2 yr. __ mo.	16 yr. __ mo.	<input checked="" 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): 2013							

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*

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

*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 checked="" type="checkbox"/>	Other	<u>2</u> yr. __ mo.	<u>16</u> yr. __ mo.	<input checked="" type="checkbox"/>	<input checked="" 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 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:

\_\_\_\_\_  
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: Psoriatic Arthritis****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

**When children first present with juvenile idiopathic arthritis, it is difficult to know whether they will develop into the psoriatic arthritis subtype. A history of psoriasis, dactylitis, ankle or toe arthritis, and DRB1\*11/12 allele status increases the likelihood of PsA, however few patients have enough features to be distinguished as PsA during childhood. Retrospective analyses of JIA cohorts have estimated that less than 10% of JIA patients turn out to have PsA (Fiato, J Rheum 2009).**

- 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,

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

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.*

**Attachment A**

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

**Indication #3: Ankylosing Spondylitis****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

**When children first present with juvenile idiopathic arthritis, it is difficult to know whether they will develop into the ankylosing spondylitis subtype. Most children do not present with the pathognomonic features of AS – they do not present with inflammatory arthritis in the spine, and inflammatory disease of the sacroiliac joints is an infrequent or late finding. Children with spondyloarthritis are a minor fraction of JIA overall, and of these children, most have arthritis related to inflammatory bowel disease or reactive arthritis.**

- 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,

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.

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.

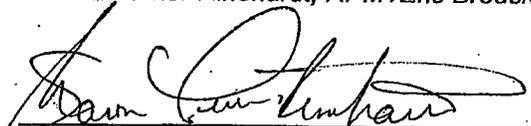
Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*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:**

Sharon Turner-Rinehardt, RPM /Eric Brodsky, MO



Regulatory Project Manager

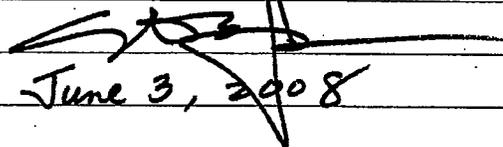
**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700**

(Revised: 6/2008)

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

### Debarment Certification

Centocor, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Name	<u>Stella S. Jones, Ph.D</u>
Title	<u>Vice President, Worldwide Regulatory Affairs</u>
Signature	<u></u>
Date	<u>June 3, 2008</u>

**NDA/BLA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

Application Information		
NDA # BLA# 125289	NDA Supplement #-S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Simponi Established/Proper Name: Golimumab Dosage Form: subcutaneous Strengths: 50 mg		
Applicant: Centocor, Inc. Agent for Applicant (if applicable):		
Date of Application: June 24, 2008 Date of Receipt: June 24, 2008 Date clock started after UN:		
PDUFA Goal Date: April 24, 2009	Action Goal Date (if different):	
Filing Date: August 23, 2008 Date of Filing Meeting: August 5, 2008		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): Rheumatoid Arthritis, Psoriatic Arthritis and Ankylosing Spondylitis		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>Refer to Appendix A for further information.</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical disease Priority review voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input checked="" type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 9925, 12723 and 12729	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ora/compliance_ref/aip.html">http://www.fda.gov/ora/compliance_ref/aip.html</a></i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
If yes, explain:	
If yes, has OC/DMPQ been notified of the submission?	<input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
Comments:	
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	<input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? <i>(NDAs/NDA efficacy supplements only)</i></p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES # years requested: <input type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use <i>(NDAs only)</i>:</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>505(D)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i></p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
<p><b>Format and Content</b></p>			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>			
<p>If electronic submission: <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If electronic submission, does it follow the eCTD guidance? (<a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>)</p> <p>If not, explain (e.g., waiver granted):</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input checked="" type="checkbox"/> pagination  <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Debarment Certification</b>	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	
<p><b>Comments:</b></p>	
<p><b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b></p>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p>	<p><input type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	
<p><b>Financial Disclosure</b></p>	
<p>Financial Disclosure forms included with authorized signature?</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p>	
<p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>	
<p><b>Comments:</b></p>	
<p><b>Pediatrics</b></p>	
<p><b>PREA</b></p>	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p>	<p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• <i>If no, request in 74-day letter.</i></li> <li>• <b>If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</b></li> </ul>	<p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><b>Comments: A request for a partial waiver and deferral is included but the Sponsor did not include a pediatric plan.</b></p>	

<b>BCPA (NDAs/NDA efficacy supplements only):</b>	
Is this submission a complete response to a pediatric Written Request?  <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
<b>Prescription Labeling</b>	
Check all types of labeling submitted.  <b>Comments:</b>	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format?  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
Package insert (PI) submitted in PLR format?  <b>If no, was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request?</b>  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? ( <i>send WORD version if available</i> )	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
REMS consulted to OSE/DRISK?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES Dates: April 6, May 16, 17, and 19, 2005 <input type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES Date(s): September 21, 2007 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** August 5, 2008

**NDA/BLA #:** 125289

**PROPRIETARY/ESTABLISHED NAMES:** SIMPONI (golimumab)

**APPLICANT:** Centocor, Inc.

**BACKGROUND:** This is a monoclonal antibody indicated for rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis.  
*(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)*

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sharon Turner-Rinehardt	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Sarah Okada		Y
Clinical	Reviewer:	Eric Brodsky	Y
	TL:	Sarah Okada	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
Labeling Review (for OTC products)	Reviewer:		
	TL:		
OSE	Reviewer:	Carlos Mena-Grillasca Kendra Worthy	Y Y
	TL:	Kristina Arnwine	Y
Clinical Microbiology (for antimicrobial products)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Lei Zhang	Y
	TL:	Suresh Doddapaneni	N
Biostatistics	Reviewer:	Joan Buenconsejo Jonathan Norton	Y Y
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Gary Bond	Y
	TL:	Adam Wasserman	Y
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Kurt Brorson	Y
	TL:	Kathleen Clouse	Y
Facility ( <i>for BLAs/BLA supplements</i> )	Reviewer:	Kalavati Suvarna Patricia Hughes	Y Y
	TL:		
Microbiology, sterility ( <i>for NDAs/NDA efficacy supplements</i> )	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Susan Leibanhaunt	Y
	TL:	Constance Lewin	N
Other reviewers			

**OTHER ATTENDEES:**

505(b)(2) filing issues?	<input checked="" type="checkbox"/> Not Applicable
If yes, list issues:	<input type="checkbox"/> YES
	<input type="checkbox"/> NO
Per reviewers, are all parts in English or English translation?	<input checked="" type="checkbox"/> YES
If no, explain:	<input type="checkbox"/> NO

<p><b>Electronic Submission comments</b></p> <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: This biologic is not the first in its class.
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>BIostatistics</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Sterile product?</li> </ul> <p>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO

<b>FACILITY (BLAs only)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Curtis Rosebraugh  <b>GRMP Timeline Milestones:</b> see GRMP timeline sheet  <b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

**ADRA Rev #1 of Action Package for BLA 125289, Simponi (golimumab), 50 mg syringe and 50 mg autoinjector**

Reviewer: Lee Ripper, ODE II

Date received: April 3, 2009

Date of review: April 10, 2009

Date original BLA received: June 24, 2008

UF goal date: April 24, 2008

*Leah Ripper 4/24/09*

Proposed Indication: RA in combo with MTX, psoriatic arthritis alone or in combo with MTX, ankylosing spondylitis

Action type: AP

RPM: Sharon Turner-Rinehardt

Drug Classification: S

Debarment Certification: AC, signed and dated 6-3-08

Financial Disclosure: The MOR page 19 is ambiguous as to whether or not outcome payments were among the types of financial interests disclosed. I reviewed the financial disclosure section of the application. There were no disclosed outcome payments. All financial interests were SPOOS or equity interest.

Safety Update: 10-21-08

Clinical Inspection Summary: 2-10-09, no regulatory violations noted, data may be used in support of AP.

DMEPA Review of Proprietary Name: Simponi AC 2-18-09.

DMEPA Review of Carton and Container Labels: 3-20-09, multiple comments

DRISK Review of MedGuide and Patient Instructions for Use: 3-20-09, multiple comments

DDMAC Review of PI and labels: 2-11-09, multiple comments

DDMAC Review of MedGuide: 1-30-09, multiple comments

SEALD Review of PLR: None

EA: Categorical exclusion claimed

EER: AC per email dated 3-25-09 from Marisa Stock

PSC Mtg: Included in WU Mtg, see memo dated 3-5-09

REMS: Consists of MedGuide, Communication Plan, and timetable of assessments.

CDTL Review: Dr. Okada, CM 3-31-09

PMRs: PREA study in 2-16 yo.

PMCs: 1. Optimize the existing assay for adventitious virus contamination or develop a new assay. 2. Drug-drug interaction studies to assess the potential effect of golimumab on cyt P450 substrate drugs. 4/24: The sponsor responded with revised labeling. The review team accepted the labeling revision and determined that PMC #2 was no longer needed as the revised wording was essentially the same as would have resulted had a drug-drug interaction been shown.

ADP/T review by Paul Brown, CM 3-26-09

**Turner-Rinehardt, Sharon**

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**From:** Turner-Rinehardt, Sharon  
**Sent:** Thursday, April 23, 2009 6:03 PM  
**To:** 'Paxson, Bethany [CNTUS]'  
**Subject:** RE: BLA 125289 Golimumab: FDA Revisions on Labeling  
**Importance:** High  
**Sensitivity:** Confidential  
**Attachments:** FDA Revisions\_4nd Round\_ 042309.pdf

Dear Bethany,  
Please see the revised wording proposed for the labeling. Also, please make sure that there are 2 spaces after every period in the label. Regarding the word "revised" at the end of the labeling, the word "revised" should be maintained as this is the correct language. I ask that you provide a response to our revisions by 10 am, Friday, April 24, 2009. If you have any questions, please contact me.

Also, as a follow-up to our telephone conversation, we are not requiring any PMRs for this application.

Regards,  
Sharon

*Sharon Turner-Rinehardt*  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and Rheumatology Products  
Email: sharon.turner-rinehardt@fda.hhs.gov

---

**From:** Paxson, Bethany [CNTUS] [mailto:BPaxson@its.jnj.com]  
**Sent:** Thursday, April 23, 2009 1:44 PM  
**To:** Turner-Rinehardt, Sharon  
**Subject:** RE: BLA 125289 Golimumab: FDA Revisions and Comments on Labeling  
**Importance:** High  
**Sensitivity:** Confidential

Hi Sharon,

Attached are our comments to your last round of revisions. As before, we have accepted those edits from the FDA that we were in agreement with and have shown in track changes any additional edits/revisions we are proposing. The CYP450 wording is included as track changes, however we agree with FDA's proposed revisions. Some minor points to note...now that the label is consistent in using the TNF-blocker terminology, we have gone through and ensured that each occurrence includes the hyphen. This is shown in track changes. In the PIFU for the Autoinjector, we moved

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b(4)

Please let me know if you have any questions or need anything else from me. Do you think we will receive

4/23/2009

Appears This Way  
On Original

**Turner-Rinehardt, Sharon**

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**From:** Turner-Rinehardt, Sharon  
**Sent:** Wednesday, April 22, 2009 7:04 PM  
**To:** 'Paxson, Bethany [CNTUS]'  
**Subject:** BLA 125289 Golimumab: FDA Revisions and Comments on Labeling  
**Importance:** High  
**Sensitivity:** Confidential  
**Attachments:** FDA Revisions\_3rd Round\_ 042209.pdf

Dear Bethany,  
Please find attached our proposed revisions with comments to your revised labeling dated April 21, 2009. We have accepted your revisions that the Division has found acceptable in the pdf document. I ask that you provide a response to our revisions by 1pm, Thursday, April 23, 2009 or sooner if possible. If you have any questions, please contact me.

Regards,  
Sharon

*Sharon Turner-Rinehardt*  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and Rheumatology Products  
Email: sharon.turner-rinehardt@fda.hhs.gov

4/23/2009

**Turner-Rinehardt, Sharon**

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**From:** Paxson, Bethany [CNTUS] [BPaxson@its.jnj.com]  
**Sent:** Wednesday, April 22, 2009 11:43 AM  
**To:** Turner-Rinehardt, Sharon  
**Subject:** RE: BLA 125289 Simponi: Response to Chemistry PMC  
**Importance:** High  
**Sensitivity:** Confidential

Hi Sharon,

Please see our response to the Chemistry PMC. This should address the Agency's request, however please let me know if anything else is needed. Regarding the Clinical Pharmacology PMC, I will respond to you in a separate email later.

**Centocor commits to optimize the existing adventitious virus assay or develop an improved assay for use at all contract locations performing adventitious virus contamination testing of unprocessed bulk harvest.**

**Study Completion and Final Report Submission: April 2010**

Thanks!  
Best regards,  
Bethany  
*Bethany Paxson*  
*Senior Director*  
*Worldwide Regulatory Affairs*  
*Centocor, Inc.*  
*Phone: (610) 651-6979*  
*Fax: (610) 651-6123*  
*Email: bpaxson@its.jnj.com*

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**-----Original Message-----**

**From:** Turner-Rinehardt, Sharon [mailto:Sharon.Turner-Rinehardt@fda.hhs.gov]  
**Sent:** Tuesday, April 21, 2009 6:10 PM  
**To:** Paxson, Bethany [CNTUS]  
**Subject:** RE: BLA 125289 Simponi: Response to Chemistry PMC  
**Importance:** High  
**Sensitivity:** Confidential

Dear Bethany,

This response is not a commitment to conduct the PMC as stated in the April 20, 2009 email. We are not asking for a PMC to conduct a review of the assay procedures but to conduct the assay. For this application to move forward, you must provide an agreement to conduct the assay as stated in the email or provide a rationale for not conducting the PMC as stated.

Regards,  
Sharon

4/23/2009

**Turner-Rinehardt, Sharon**

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**From:** Turner-Rinehardt, Sharon  
**Sent:** Friday, April 17, 2009 4:45 PM  
**To:** 'Paxson, Bethany [CNTUS]'  
**Subject:** BLA 125289 Golimumab: FDA Comments on Package Insert  
**Importance:** High  
**Sensitivity:** Confidential  
**Attachments:** FDA Revisions for PI\_2nd Round\_ 041709.pdf

Dear Bethany,  
Please find attached our proposed revisions with comments to your revisions dated April 3, 2009. We have accepted your revisions that the Division has found acceptable in the pdf document. I ask that you provide a response to our revisions by 4pm, Tuesday, April 21, 2009 or sooner if possible. If you have any questions, please contact me.

Regards,  
Sharon

*Sharon Turner-Rinehardt*  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and Rheumatology Products  
Email: sharon.turner-rinehardt@fda.hhs.gov

4/23/2009

## Turner-Rinehardt, Sharon

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**From:** Turner-Rinehardt, Sharon  
**Sent:** Wednesday, April 15, 2009 1:06 PM  
**To:** 'Paxson, Bethany [CNTUS]'  
**Subject:** RE: BLA 125289 Simponi: PMCs

**Importance:** High  
**Sensitivity:** Confidential

Dear Bethany,  
We are requesting the following PMCs for the golimumab application. I ask that you review the PMCs and provide your agreement as well as the timelines for each study by 3pm, Friday, March 17, 2009.

### Clinical Pharmacology

To conduct in vivo drug interaction studies in patients with elevated TNF $\alpha$  levels to assess the potential effect of golimumab on cytochrome P450 substrate drugs. A "cocktail" study with multiple P450 probe substrate drugs may be considered.

**Protocol Submission:**  
**Study Start:**  
**Study Completion:**  
**Final Report Submission:**

### Chemistry

To optimize the existing assay or develop an improved assay for detection of adventitious virus contamination in the unprocessed bulk harvest performed at ██████████ **b(4)**

**Study Completion:**  
**Final Report Submission:**

If you have any questions, please contact me.

Regards,  
Sharon

*Sharon Turner-Rinehardt*  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and Rheumatology Products  
Office of Drug Evaluation II  
Phone: (301) 796-2254  
Fax: (301) 796-9713  
Email: sharon.turner-rinehardt@fda.hhs.gov

**Turner-Rinehardt, Sharon**

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**From:** Turner-Rinehardt, Sharon  
**Sent:** Tuesday, April 14, 2009 8:31 PM  
**To:** 'Paxson, Bethany [CNTUS]'  
**Subject:** BLA 125289 Simponi: Revised REMS and Medguide and PIFU  
**Importance:** High  
**Sensitivity:** Confidential  
**Attachments:** BLA 125289 REMS Revisions\_041409.pdf; FDA Revisions\_Medguide and PIFU\_2nd Round\_041409.pdf

Dear Bethany,  
Please find attached the revisions for the REMS as well as the Medication Guide and Patient Instructions for Use.

Regarding the REMS, the Division of Risk Management (DRISK) has completed their review of your proposed REMS and requested the changes noted in the attached document for the REMS to be acceptable. The following is also required for this application. When you submit the revised documents for the REMS, you should also state that you agree to the two items below.

\_\_\_\_\_

**b(4)**

Regarding the Medication Guide and Patient Instructions for Use, there are some minor changes and an addition of a figure in the PIFU.

I anticipate sending the remaining package insert with our revisions to you by Thursday or Friday. You may wait for the package insert and respond to the entire label at the same time. However, I would like a response to the REMS material by 3 pm (EST), Friday, April 17, 2009. If you have any questions, please contact me.

Regards,  
Sharon

*Sharon Turner-Rinehardt*  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and Rheumatology Products  
Email: [sharon.turner-rinehardt@fda.hhs.gov](mailto:sharon.turner-rinehardt@fda.hhs.gov)

**Turner-Rinehardt, Sharon**

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**From:** Turner-Rinehardt, Sharon  
**Sent:** Friday, March 27, 2009 5:02 PM  
**To:** 'Paxson, Bethany [CNTUS]'  
**Subject:** BLA 125289 Golimumab: Revised DRAFT Package Insert, MedGuide and Patient Instructions  
**Importance:** High  
**Sensitivity:** Confidential  
**Attachments:** Revised PI and MedGuide for Sponsor\_032709.pdf

Dear Bethany,

Please find attached our **DRAFT** revised version of the package insert, medguide and patient instructions. Please note that our management has not completed reviewing these items; therefore, there may be additional revisions. However, we wanted to provide you with adequate time to review our revisions. I ask that you provide concurrence, comments and/or edits by 5pm (EST), Friday, April 3, 2009. I am aware that the figures requested in the patient instruction sheets may require additional time. I ask that you provide me with a timeframe that these items may be completed keeping in mind that these items will need to be reviewed again before the action date. If you have any questions, please contact me.

Regards,  
Sharon

*Sharon Turner-Rinehardt*  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and Rheumatology Products  
Phone: (301) 796-2254  
Fax: (301) 796-9723  
Email: sharon.turner-rinehardt@fda.hhs.gov

**Hughes, Patricia**

---

**From:** Stock, Marisa  
**Sent:** Wednesday, March 25, 2009 4:10 PM  
**To:** Hughes, Patricia  
**Cc:** CDER-TB-EER  
**Subject:** RE: TB-eer final for BLA 125289 golimumab from Centocor

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Please see the original request below for the compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of BLA 125289 at this time.

**Marisa Stock**  
Consumer Safety Officer  
Food and Drug Administration  
CDER/OC/DMPQ  
10903 New Hampshire Avenue  
Building 51, Room 4243  
Silver Spring, MD 20993  
Phone: (301) 796-4753

---

**From:** Hughes, Patricia  
**Sent:** Thursday, March 19, 2009 8:08 AM  
**To:** CDER-TB-EER  
**Cc:** Suvarna, Kalavati; Hoyt, Colleen  
**Subject:** TB-eer final for BLA 125289 golimumab from Centocor

Please conduct the following final assessment the following sites for the BLA 125289 for golimumab from Centocor. The PDUFA date is April 24, 2009.

The sites are as follows:

\_\_\_\_\_

b(4)

CNTO 148 drug substance is manufactured, and the PFS are release tested at (site was recently inspected by BMT in 2009):

Centocor  
Einsteinweg 101  
2333 CB Leiden  
The Netherlands  
FEI= 3002806632

Inspected January 28 - February 3, 2009 by the Biotech Manufacturing Team and considered acceptable after review by the International Compliance Branch. The inspection was classified VAI.

CNTO 148 PFS are assembled with the Centocor Autoinjector or \_\_\_\_\_ at Cilag. This site is also responsible for the functional and sterility test of stability samples. The site information is as follows:

b(4)

Cilag AG  
Hochstrasse 201

8205 Schaffauser

Switzerland

FEI= 3002806695

Inspected June 21-28, 2007 and classified VAI. The SVS profile was covered and is acceptable.

Labeling and packaging of the PFS assembled occur at:

Ortho-McNeil Pharmaceuticals, Inc.

1000 Route 202

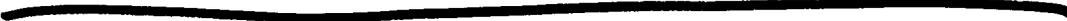
Raritan, NJ 08869

USA

FEI=2211100

Inspected January 5-15, 2009 and classified VAI. This site is an acceptable packer/repacker for profiles SVL and SVS.

Sterility testing:



b(4)

Thank you.

Patricia

**Turner-Rinehardt, Sharon**

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**From:** Turner-Rinehardt, Sharon  
**Sent:** Tuesday, March 10, 2009 6:16 PM  
**To:** 'Paxson, Bethany [CNTUS]'  
**Subject:** RE: BLA 125289 Golimumab: REMS Proposal Information Request  
**Sensitivity:** Confidential  
**Attachments:** Golimumab\_Appendix 1 riskcomm\_031009.pdf

Hi Bethany,

As a follow-up to our telephone conversation, no, the items in section 4C are not required on March 20. This information will be required at a later date if the application is approved.

Also, please find attached as discussed in our telephone conversation, our edits to Appendix 1. I ask that you submit your comments/edits or your agreement with the changes with the other items requested on March 20. If you have any other questions, please contact me.

Regards,  
Sharon

*Sharon Turner-Rinehardt*

Regulatory Health Project Manager

Division of Anesthesia, Analgesia and Rheumatology Products

Phone: (301) 796-2254

Fax: (301) 796-9723

Email: sharon.turner-rinehardt@fda.hhs.gov

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**From:** Paxson, Bethany [CNTUS] [mailto:BPaxson@its.jnj.com]  
**Sent:** Tuesday, March 10, 2009 5:53 PM  
**To:** Turner-Rinehardt, Sharon  
**Subject:** RE: BLA 125289 Golimumab: REMS Proposal Information Request  
**Importance:** High  
**Sensitivity:** Confidential

Hi Sharon,

In reviewing this Information Request in detail today, we would like to ask one question of clarification. In Item 4.C. below, we would like to clarify FDA's expectation regarding the timeframe for providing the detailed plans on the items i. through x. Are these expected on March 20 as well?

Many thanks!

Best regards,

Bethany

*Bethany Paxson*

*Senior Director*

*Worldwide Regulatory Affairs*

*Centocor, Inc.*

*Phone: (610) 651-6979*

*Fax: (610) 651-6123*

*Email: bpaxson@its.jnj.com*

3/25/2009

**Turner-Rinehardt, Sharon**

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**From:** Turner-Rinehardt, Sharon  
**Sent:** Monday, March 09, 2009 1:16 PM  
**To:** 'Paxson, Bethany [CNTUS]'  
**Subject:** BLA 125289 Golimumab: REMS Proposal Information Request  
**Importance:** High  
**Sensitivity:** Confidential

Dear Bethany,  
The Division of Risk Management (DRISK) has reviewed your proposed REMS and have the following comments. This information will also be provided in a formal letter; however, in essence of time, I am providing the information via email now. I ask that you provide all the requested information by 5 pm, Friday, March 20, 2009.

Resubmit the revised Proposed REMS with appended materials, and the REMS Supporting Document. Provide a track changes and a clean version of all revised materials and documents. Submit your proposed REMS and other materials in WORD format.

b(4)

4 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Administrative- 14

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** March 5, 2009

**TO:** File

**FROM:** Sharon Turner-Rinehardt, Regulatory Health Project Manager *SR*

**SUBJECT:** **Pre-Approval Safety Conference**  
BLA 125289 Simponi (Golimumab)

In lieu of a separate preapproval safety conference with OSE staff, the Division decided to include this as part of the Wrap-Up meeting for BLA 125289 which was held on February 19, 2009. Members of the OSE staff present at the meeting were Chris Wheeler Manager, Ann McMahon, Kendra Worthy, Kate Heinrich and Carlos Mena-Grillasca. Also present at the meeting were the following: Bob Rappaport, Rigoberto Roca, Kurt Brorson, Gary Bond, Suresh Doddapaneni, Dionne Price, Thomas Permutt, Jonathan Norton, Lei Zhang, Joan Bueconsejo, Adam Wasserman, Leah Ripper, Diana Walker, Patricia Hughes, Kalavati Suvarna, David Frucht and via telephone were the following: Curtis Rosebraugh, Kathleen Clouse and Pandu Soprey.

During the meeting, the clinical reviewer presented a comprehensive overview of the safety profile of golimumab. OSE asked a question regarding the frequency of the malignancies present with the golimumab-treated patients compared to the control-treated patients in the Phase 2 asthma trial and the clinical reviewer stated that the frequency of these malignancies may be due to the higher dose of golimumab and the use of greater steroid doses. OSE did not have any other questions and was satisfied with the safety information presented for golimumab.

**Appears This Way  
On Original**

**Turner-Rinehardt, Sharon**

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**From:** Turner-Rinehardt, Sharon  
**Sent:** Friday, February 27, 2009 2:48 PM  
**To:** 'Paxson, Bethany [CNTUS]'  
**Subject:** Golimumab BLA 125289: Status Update  
**Importance:** High  
**Sensitivity:** Confidential

Dear Bethany,  
The review of the application is progressing.

Regarding the tradename, SIMPONI, the Division of Medication Error and Analysis (DMEPA) has completed their review and have found the name acceptable. Also, regarding the name Smartject for the autoinjector, Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed Centocor's appeal and have decided to allow the name to be used for the autoinjector.

If you have any other questions, please contact me.

Regards,  
Sharon

*Sharon Turner-Rinehardt*  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and Rheumatology Products  
Phone: (301) 796-2254  
Fax: (301) 796-9713  
Email: sharon.turner-rinehardt@fda.hhs.gov

**Turner-Rinehardt, Sharon**

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**From:** Mena-Grillasca, Carlos  
**Sent:** Wednesday, February 18, 2009 10:42 AM  
**To:** Turner-Rinehardt, Sharon  
**Cc:** Wheeler, Chris; Holquist, Carol A; Toyer, Denise P; Rappaport, Bob A  
**Subject:** BLA 125,289 - Golimumab (RCM#2008-1069)

Hello Sharon,

This email is to notify you that the Division of Medication Error and Analysis (DMEPA) has completed the assessment of the proposed name Simponi (BLA 125,289; Golimumab). DMEPA will allow the use of the name Simponi for this product.

Please share the above with your team and let us know whether or not you concur with our assessment and if you have any concerns regarding the proposed proprietary name. Please respond with any comments within 14 days of receipt of this communication.

Thank you,

Carlos M Mena-Grillasca  
Acting Team Leader  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
CDER / FDA  
10903 New Hampshire Avenue  
WO Bldg. 22 Rm. 4433  
Silver Spring, MD 20993  
[carlos.mena-grillasca@fda.hhs.gov](mailto:carlos.mena-grillasca@fda.hhs.gov)  
1.301.796.4073

3/26/2009

## Turner-Rinehardt, Sharon

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**From:** Turner-Rinehardt, Sharon  
**Sent:** Monday, February 02, 2009 4:31 PM  
**To:** 'Paxson, Bethany [CNTUS]'  
**Subject:** BLA 125289 Golimumab: Information Request

**Importance:** High

Dear Bethany,  
I have the following information request:

Conduct re-randomization tests for the primary endpoints of the pivotal studies for BLA 125289 (C0524T05, C0524T06, C0524T08, C0524T09, and C0524T11) as follows: Replicate the randomization exactly as it was done before, but with new random numbers. Perform 10,000 replications for each study, then compare the primary test statistic(s) from the study to the empirical distribution(s) computed from the replications. Provide the algorithm, results, and software code.

I ask that you provide this information by noon Friday, February 6, 2009. If you have any questions, please contact me.

Regards,  
Sharon

*Sharon Turner-Rinehardt*  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and Rheumatology Products  
Phone: (301) 796-2254  
Fax: (301) 796-9713  
Email: [sharon.turner-rinehardt@fda.hhs.gov](mailto:sharon.turner-rinehardt@fda.hhs.gov)

## Turner-Rinehardt, Sharon

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**From:** Turner-Rinehardt, Sharon  
**Sent:** Friday, January 23, 2009 6:31 PM  
**To:** 'Paxson, Bethany [CNTUS]'  
**Subject:** BLA 125289 Simponi - Information Request

**Importance:** High

Dear Bethany,

Please provide the master file number for the autoinjector and a letter of authorization to access the master file. I ask that you provide this information as soon as possible.

Regards,  
Sharon

*Sharon Turner-Rinehardt*

Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and Rheumatology Products  
Phone: (301) 796-2254  
Fax: (301) 796-9723  
Email: [sharon.turner-rinehardt@fda.hhs.gov](mailto:sharon.turner-rinehardt@fda.hhs.gov)

**Turner-Rinehardt, Sharon**

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**From:** Turner-Rinehardt, Sharon  
**Sent:** Tuesday, December 16, 2008 3:22 PM  
**To:** 'Paxson, Bethany [CNTUS]'  
**Subject:** BLA 125289 Golimumab: Question Regarding Study Director Involved with Discovery Report  
**Importance:** High  
**Sensitivity:** Confidential

Dear Bethany,

In a letter received from Centocor dated December 9, 2008, it was requested that the Division not consider Discovery Report DIS.RES.DRR.010 as part of the BLA review because the data from the study was compromised by the study director. Was the study director involved in any other study submitted for review for the BLA? I ask that you provide a response as soon as possible.

Regards,  
Sharon

*Sharon Turner-Rinehardt*

Regulatory Health Project Manager

Division of Anesthesia, Analgesia and Rheumatology Products

Phone: (301) 796-2254

Fax: (301) 796-9723

Email: [sharon.turner-rinehardt@fda.hhs.gov](mailto:sharon.turner-rinehardt@fda.hhs.gov)

3/25/2009

## Turner-Rinehardt, Sharon

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**From:** Turner-Rinehardt, Sharon  
**Sent:** Tuesday, November 25, 2008 7:15 PM  
**To:** 'Paxson, Bethany [CNTUS]'  
**Subject:** BLA 125289 Golimumab: Information Request

**Importance:** High

Dear Bethany,  
I have the following information request for BLA 125289:

1. Regarding Study C0524T06, subject C0524T06-6401-60442 was excluded under sensitivity analysis 4 for the ACR20 (source: ACR20S4 in SUBJEF data set). According to DEFINE.PDF, "Subjects who had 3 or more consecutive oral doses missed prior to Week 14, will be excluded unless they were a treatment failure..." Based on the values in the EXPOSURE data set, the longest gap in dosing before week 14 was from November 30 to December 21 (21 days). Hence this subject missed no more than two weekly doses prior to week 14. Moreover, this subject was not a treatment failure. Explain why this subject was excluded under sensitivity analysis 4.
2. Describe any measures taken to maintain the blind among investigators during the supply shortage for Golimumab.

I ask that you respond by 3pm, Thursday, December 4, 2008. If you have any questions, please contact me.

Regards,  
Sharon

*Sharon Turner-Rinehardt*

Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and Rheumatology Products  
Phone: (301) 796-2254  
Fax: (301) 796-9723  
Email: [sharon.turner-rinehardt@fda.hhs.gov](mailto:sharon.turner-rinehardt@fda.hhs.gov)

**Turner-Rinehardt, Sharon**

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**From:** Turner-Rinehardt, Sharon  
**Sent:** Friday, November 07, 2008 9:18 AM  
**To:** 'Paxson, Bethany [CNTUS]'  
**Subject:** BLA 125289: Follow up to phone message/eval and Information Request  
**Importance:** High

Hello Bethany,

Thank you for the update regarding the timing of the REMS. Also, regarding the human factor study, the information that was submitted on the CD was not in eCTD format and the group that loads these submission would like for this submission to be formatted in this manner, if possible, because it has caused problems with the system when loaded. So, is it possible to reformat this information in eCTD?

Also, the SAS code was provided for the following studies associated with BLA 125289: C0524T05, C0524T06, C0524T08, C0524T09, and C0524T11. However, we have been unable to convert the files from PDF format to SAS format. Provide the code (macros, mockups, programs) in files that can be opened directly in SAS. I ask that you provide this information as soon as possible.

Any questions, please contact me.

Regards,  
Sharon

*Sharon Turner-Rinehardt*

Regulatory Health Project Manager

Division of Anesthesia, Analgesia and Rheumatology Products

Fax: (301) 796-9723

Email: sharon.turner-rinehardt@fda.hhs.gov

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**From:** Paxson, Bethany [CNTUS] [mailto:BPaxson@its.jnj.com]  
**Sent:** Wednesday, November 05, 2008 5:10 PM  
**To:** Turner-Rinehardt, Sharon  
**Subject:** Follow up to phone message: BLA 125289

Hi Sharon,

I hope that you are doing well. I just wanted to follow up with you to make sure that you got my voicemail regarding our targeted submission timing for the golimumab REMS. You had also mentioned that you may need some additional information related to the human factors study we previously submitted on disk. Please let me know if there is anything else that we can provide in order to facilitate the review of the golimumab BLA. As our timelines become definitive with regards to the golimumab REMS, I will keep you informed, however we are targeting end of November. I trust that you also received the pediatric development plan that was submitted on 31 October.

Thanks and best regards,  
Bethany

*Bethany Paxson*  
*Senior Director*

3/25/2009



**FILING COMMUNICATION**

Our STN: BLA 125289/0

September 5, 2008

Centocor, Inc.  
200 Great Valley Parkway  
Malvern, PA 19355

Attention: Bethany K. Paxson  
Senior Director, Global Regulatory Liaison

Dear Ms. Paxson:

This letter is in regard to your biologics license application (BLA) dated and received June 24, 2008, submitted under section 351 of the Public Health Service Act, for Simponi (golimumab).

We have completed an initial review of your application to determine its acceptability for filing. Under 21 CFR 601.2(a), we filed your application on August 23, 2008. The review classification for this application is Standard. Therefore, the user fee goal date is April 24, 2009. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

During our filing review of your application, we have identified the following potential review issues and we request that you submit the following information.

1. For each of the five individual Phase 3 trials, submit the following data: the proportion of patients who received concomitant NSAIDs or corticosteroids and the mean (SD) and median daily doses of concomitant prednisone or equivalent at Weeks 14 and 24 by treatment group.
2. Submit a MedDRA "coding dictionary," a list of all investigator verbatim terms and the preferred terms to which they were mapped including bidirectional coding (i.e., from verbatim term to preferred term and from preferred term to verbatim term).

In addition, we have identified that the ongoing long-term extensions (up to 5 years) of your five Phase 3 trials include a low and high dose regimen (i.e., 50 and 100 mg of SC golimumab once every 4 weeks, respectively). Your application only proposes the 50mg dose for approval. Clarify whether you intend to continue using the 100mg dose in the long-term extensions and if yes, provide your rationale for doing so.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a full waiver of pediatric studies for juvenile ankylosing spondylitis and patients without the polyarticular form of juvenile psoriatic arthritis. We also acknowledge receipt of your request for a deferral of pediatric studies for juvenile idiopathic arthritis from 2 to 16 years of age.

However, you did not provide a pediatric plan and a proposed timeline for the completion of such studies. Therefore, submit a pediatric development plan and the proposed timeline for each of the proposed pediatric studies and include the approximate dates for the protocol submission, study initiation and the final study report.

In addition, we have the following comments regarding the PLR labeling submitted with this BLA. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

1. For biologic products, the dosage form and route of administration must be on the next line (underneath the proper name) in the **HIGHLIGHTS OF PRESCRIBING INFORMATION** section (See 21 CFR 600.3 (k) and Section 351 of the PHS Act.)
2. Move the references for rheumatoid arthritis and psoriatic arthritis in the Highlights **INDICATION AND USAGE** section before the colon.
3. Include “Revised: Month/Year” at the end of the **HIGHLIGHTS**. The revision date will be month/year the application is approved.
4. Add the boxed warning statement “**WARNING: RISK OF SERIOUS INFECTIONS**” to the beginning of the Full Prescribing Information (FPI): Contents\* section.
5. A horizontal line must separate the Contents and FPI [see 21 CFR 201.57(d)(2)].
6. Move all references in the FPI to be enclosed by the period at the end of the sentence.

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. In the meantime, we encourage you to submit revised labeling that meets the half page requirement.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted,

expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we will advise you in writing of any action we have taken and request additional information if needed.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Sharon Turner-Rinchardt, Regulatory Health Project Manager, at (301) 796-2254.

Sincerely,

A handwritten signature in black ink, appearing to read 'Bob Rappaport', with a large, sweeping flourish extending to the right.

Bob Rappaport, M.D.  
Director  
Division of Anesthesia, Analgesia and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

## Turner-Rinehardt, Sharon

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**From:** Turner-Rinehardt, Sharon  
**Sent:** Monday, August 11, 2008 5:30 PM  
**To:** 'Paxson, Bethany [CNTUS]'  
**Subject:** BLA 125289 Golimumab Information Request  
**Importance:** High

Dear Bethany,

Provide a sample (i.e. working model) of the pre-filled syringe. Also, provide the information from the Simulated Use Study (SUS) and the Human Factors studies referenced in the Risk Mitigation Plan, Module 1.16, page 99. I ask that you provide this information by Monday, August 18, 2008. If you have any questions, contact me.

Regards,  
Sharon

*Sharon Turner-Rinehardt*

Regulatory Health Project Manager  
Division of Anesthesia, Analgesia and Rheumatology Products  
Phone: (301) 796-2254  
Fax: (301) 796-9722/9723  
Email: [sharon.turner-rinehardt@fda.hhs.gov](mailto:sharon.turner-rinehardt@fda.hhs.gov)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

Our STN: BLA 125289/0

**BLA ACKNOWLEDGEMENT**

Centocor, Inc.  
200 Great Valley Parkway  
Malvern, PA 19355

JUL 8 2008

Attention: Bethany K. Paxson  
Senior Director, Global Regulatory Liaison

Dear Ms. Paxson:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act (PHS Act) for the following:

**Name of Biological Product:** Simponi (Golimumab)

**Date of Application:** June 24, 2008

**Date of Receipt:** June 24, 2008

**Our Submission Tracking Number (STN):** BLA 125289/0

**Proposed Use:** Treatment of Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

The BLA Submission Tracking 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  
Therapeutic Biological Products Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not

obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

If you have any questions, call me at (301) 796-2254.

Sincerely,

A handwritten signature in cursive script, appearing to read "Sharon Turner-Rinehardt".

Sharon Turner-Rinehardt  
Regulatory Health Project Manager  
Division of Anesthesia, Analgesia, and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 9925, IND 12723, and IND 12729

Centocor, Inc.  
200 Great Valley Parkway  
Malvern, PA 19355

Attention: Bethany Paxson  
Director, Worldwide Regulatory Affairs

Dear Ms. Paxson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Golimumab (CNTO 148).

We also refer to the meeting between representatives of your firm and the FDA on August 21, 2007. The purpose of the meeting was to discuss the proposed content and format of the golimumab BLA; and to resolve any outstanding issues and identify any additional information necessary to support a marketing application for golimumab.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1251.

Sincerely,

*{See appended electronic signature page}*

Lisa Malandro, MBA  
Regulatory Health Project Manager  
Division of Anesthetic, Critical Care,  
and Addiction Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

## SPONSOR MEETING AGENDA

**MEETING DATE:** August 21, 2007  
**TIME:** 1:30 pm  
**LOCATION:** White Oak, Conference Room 1315  
**APPLICATIONS:** IND 9925, IND 12723, and IND 12729  
**PRODUCT:** Golimumab (CNTO 148)  
**INDICATIONS:** \_\_\_\_\_ Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), and Ankylosing Spondylitis (AS)  
**SPONSOR:** Centocor, Inc.  
**TYPE OF MEETING:** Type B; Pre-BLA  
**MEETING CHAIR:** Jeffrey Siegel, MD, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)  
**MEETING RECORDER:** Lisa Malandro, MBA, Regulatory Project Manager

b(4)

FDA Attendees	Title
Curtis Rosebraugh, MD	Deputy Director, Office of Drug Evaluation II
Bob Rappaport, MD	Director, DAARP
Patrick Swann, PhD	Deputy Director, Division of Monoclonal Antibodies (DMA)
Daniel Mellon, PhD	Supervisory Pharmacologist
Jeffrey Siegel, MD	Team Leader, Rheumatology
Dionne Price, PhD	Team Leader, Biostatistics
Kurt Brorson, PhD	Biologist, DMA
Gary Bond, PhD	Pharmacology/Toxicology Reviewer
Eric Brodsky, MD	Clinical Reviewer
Katherine Meaker, PhD	Biostatistician
Srikanth Nallani, PhD	Clinical Pharmacology Reviewer
Patricia Love, MD	Associate Director, Office of Combination Products
Peter Diak	Safety Evaluator, Office of Safety and Epidemiology
Lisa Malandro, MBA	Regulatory Health Project Manager
Centocor Attendees	Title
Dan Baker, MD	Vice President, Clinical R&D
Michael Elliott, MD	Senior Vice President, Clinical R&D
John Han, PhD	Associate Director, Biostatistics
Thomas Hogan	Vice President, Worldwide Regulatory Affairs, CMC
Stella Jones, PhD	Vice President, Worldwide Regulatory Affairs
Francesca Lawson, MD	Senior Director, Clinical R&D
Michael Mack, PhD	Assistant Director, Biostatistics
Douglas Mead, Director	Worldwide Regulatory Affairs, CMC
Salvatore Morello, MS	Associate Director, Worldwide Regulatory Affairs
Bethany Paxson	Director, Worldwide Regulatory Affairs
Mahboob Rahman, MD, PhD	Senior Director, Clinical R&D
Richard Siegel, PhD	Vice President, Pharmaceutical Development
Linda Vega	Senior Manager, Worldwide Regulatory Affairs
David Volkin, PhD	Senior Director, Analytic and Drug Product Development
Michael Xu, PhD	Assistant Director, Clinical Pharmacology and Experimental Medicine
Anna Beutler, MD	Senior Director, Clinical R&D

Michael Brennan	Vice President, Worldwide Regulatory Affairs
Jerry Boscia, MD	Senior Vice President, Clinical R&D
Thomas Dolan	Senior Director, GBSC Global Quality Operations
Pauline Martin, PhD	Associate Director, Toxicology
Donald Neblock, PhD	Senior Director, Bioprocess Sciences
Karen Nelson	Senior Director, Worldwide Regulatory Affairs, CMC
Amy Rahn,	Senior Manager, Clinical Research Programming
Glen Tolman, PhD	Senior Director, Pharmaceutical Technology
George Treacy, PhD	Vice President, Toxicology
Kevin Wanczyk	Manager, Worldwide Regulatory Affairs, CMC
Carrie Wagner, PhD	Senior Director, Clinical Pharmacology and Experimental Medicine

**MEETING OBJECTIVES:** To seek guidance and agreement from the Agency pertaining to the proposed content and format of the golimumab BLA; and to resolve any outstanding issues and identify any additional information necessary to support a marketing application for golimumab.

**BACKGROUND:** The Sponsor submitted a meeting request dated March 21, 2007. The meeting was granted and scheduled for August 21, 2007. The supporting background package was submitted on July 20, 2007. The Sponsor informed Lisa Malandro that they intended to focus the discussion on questions 15, 7, 6, and 2 followed by clarifications of questions 3, 4, 5, 10, and 12. All questions and Agency responses are listed below, in numerical order, for reference. Sponsor questions are in *italicized* text, Agency responses are in **bolded** text, discussion during the meeting is in normal text (i.e., DISCUSSION), and Agency's post meeting comments are in normal text (i.e., POST MEETING COMMENTS).

**MEETING MINUTES:**

*Question 1 – Adequacy of Toxicology Package*

- a) *Does the Agency concur that Centocor's complete response adequately addresses these issues?*
- b) *If so, Centocor believes that the nonclinical toxicology program outlined in this briefing package adequately supports the registration of golimumab. Does the Agency agree?*

**FDA Response:**

- 1. Yes. Include your complete responses in the Nonclinical Overview section of the original BLA submission including any additional information that may become available in the interim. Copies of primary references should be included in the Nonclinical Study Reports section of the submission.**
- 2. Yes. Your nonclinical toxicology program includes the required information needed to support registration pending review of all the information upon submission of the original BLA.**

**Additional Nonclinical Comments:**

1. Any responses are preliminary pending receipt and review of all nonclinical studies as part of the original BLA submission.
2. Include full reports for all nonclinical Pharmacology/Toxicology studies with the original BLA submission. It appears that your submission of August 25, 2006 is lacking several nonclinical reports (e.g., mouse fertility, embryo-fetal development, and pre- and post-natal development and monkey pre- and post-natal development).

*Question 2 – Clinical PK and Immunogenicity Analysis*

*Does the Agency agree that Centocor's planned PK and immunogenicity analyses in the Phase 3 studies are adequate to support the efficacy and safety analyses for the BLA submission?*

**FDA Response:**

The general approach to pharmacokinetic (PK) data analyses appears acceptable. If possible, apply the structural model developed from PK analysis of intensive sampling data from Phase 1/2 PK studies in RA/healthy subjects to the Phase 3 PK data in your analysis. If creatinine clearance data was obtained from patients, evaluate its effect on the PK of golimumab.

We recommend that you include data from Study C0524T11 in the initial submission.

Submit the following datasets to support the population PK analysis:

1. All datasets used for model development and validation should be submitted as a SAS transport file (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
2. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g., myfile\_ctl.txt, myfile\_out.txt).
3. A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, SC route clearance should be presented as CL/F (L/h) and not as THETA(1). A description of the clinical application of modeling results should be provided in the summary of the report.

**You propose to conduct efficacy analyses based on trough serum golimumab concentrations, the presence of antibodies to golimumab, and the presence of neutralizing antibodies in patients who have antibodies to golimumab in the five Phase 3 studies. Since the presence of concomitant medications (e.g., MTX) can affect the immunogenicity of TNF inhibitors (e.g., infliximab), we recommend you conduct your analyses based on assigned treatment group by randomization for each individual Phase 3 study and we recommend you exclude patients who entered the early escape phase. Furthermore, we recommend you use the pre-specified primary efficacy endpoints for your analyses.**

#### DISCUSSION

The Sponsor clarified that their population pharmacokinetic (PK) analysis focused on Phase 3 data. Although an exploratory PK evaluation of Phase 1 and 2 data was conducted, these data will only be supportive to the Phase 3 data analyses. Hence, the Phase 1, 2, and 3 data will not be combined. Dr. Nallani stated that this was an acceptable approach.

The Sponsor also plans to provide one population pharmacokinetic analysis per indication. For Rheumatoid Arthritis, Studies 5 and 6 will be pooled but Study 11 will not be included in the pooled analysis. However, all drug concentration data from Study 11 will be provided with the initial BLA submission. Dr. Nallani requested that the Sponsor submit their rationale for not including Study 11 in the pooled analysis. He also requested the Sponsor address in their BLA submission the impact of missed doses due to drug shortage on the pharmacokinetic analyses. The sponsor acknowledged the request.

For the efficacy analyses exploring the effect of PK (e.g., trough serum golimumab concentrations) and immunogenicity (e.g., the presence of antibodies to golimumab and the presence of neutralizing antibodies in patients who have antibodies to golimumab) in the five Phase 3 studies, Dr. Brodsky confirmed that, since the escape periods occurred after assessment of the primary endpoints, the exclusion of patients who entered early escape would not be relevant.

#### POST MEETING NOTE

For future meeting packages, we recommend that you include synopses of all of the Pharmacokinetic studies.

For evaluation of the relationship between the presence of antibodies to golimumab and golimumab pharmacokinetics (e.g., trough serum golimumab concentrations) and the relationship between the presence of antibodies to golimumab and safety measures in the five individual Phase 3 studies, we recommend you use the formats as presented in Tables 1 and 2 (Study 5), 3 (Study 6), 4 (Studies 9 and 11), and 5 (Study 8).

*Question 3 – Justification for 10% noninferiority margin in C0524T05*

*Does the Agency agree with Centocor's justification of a 10% margin to demonstrate the noninferiority of golimumab monotherapy versus MTX alone in ACR 50 response?*

**FDA Response:**

In your April 2007 statistical analysis plan (SAP) for Study C0524T05 (Study 5), you propose the following four-tiered testing for the first co-primary efficacy endpoint (i.e., the proportion of patients who achieve an ACR50 response at Week 24):

- 1) The primary statistical comparison (for superiority) will be between the low and high dose combination groups (i.e., golimumab 50 & MTX and golimumab 100 & MTX, respectively) with the MTX monotherapy group.
- 2) If this is significant, a comparison (for superiority) between the low-dose combination group with MTX and a comparison (for superiority) between the high-dose combination group with MTX will be performed.
- 3) If “positive tests results for the analysis” presented above are achieved then a non-inferiority analysis between the golimumab and MTX monotherapy groups will be performed. Non-inferiority of golimumab and MTX will be demonstrated if the lower bound of the 95% confidence interval (CI) is above -0.1.
- 4) If non-inferiority is declared, then a superiority analysis between the golimumab and MTX groups will be performed.

You based the selection of the 10% non-inferiority margin between the golimumab and MTX groups on preserving about 70% of the MTX treatment effect compared to placebo (ACR50 responses at Week 24 for MTX and placebo are about 33% and 0%, respectively). Presuming your other assumptions regarding the similarity of designs and target study populations are valid and the conduct of Study 5 supports a non-inferiority comparison, then a 10% noninferiority margin is acceptable.

However, you did not clarify what “analysis” needs to be positive prior to performing the non-inferiority analysis. If the high-dose combination with MTX comparison (one of your secondary analyses) is positive, then it would be acceptable to perform the third analysis (the non-inferiority analysis). However, if the high-dose combination with MTX comparison is negative, then it would not be acceptable to perform the third analysis (the non-inferiority analysis) under your tiered SAP.

It is unclear whether your non-inferiority comparison will be based on a 1-sided or 2-sided CI. If it is 1-sided, then it should be a 97.5% CI and if it is 2-sided, then it should be a 95% CI. Success of the non-inferiority comparison could support efficacy of golimumab-alone, but would not be sufficient to support a comparative claim versus MTX-alone.

*Question 4 - Overall Plans for Evaluating Efficacy Across Indications*

*Does the FDA agree with the approach to the Summary of Clinical Efficacy for each indication?*

**FDA Response:**

You propose to present summaries of clinical efficacy for each of your proposed indications [i.e., Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), and Ankylosing Spondylitis (AS)] in the Summary of Clinical Efficacy (SCE). The SCEs for the PsA and AS indications will summarize the results of the single studies for those indications. The SCE for the RA indication will summarize the results of the three RA studies; however, the results will not be pooled because the studies were performed in different RA populations. Your proposal is acceptable.

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See our responses to Question 5 regarding pooling of the subgroup efficacy analyses.

POST MEETING COMMENTS

You are proposing that golimumab be indicated for the treatment of PsA, either as monotherapy or in combination with MTX, on the basis of one study (C0524T08) where the placebo and two golimumab treatment arms will all include patients who may or may not be on concomitant MTX. In order to enable assessment of the efficacy of golimumab as monotherapy you should submit efficacy subgroup analyses based on concomitant MTX use for the three study arms.

*Question 5 - Pooled Efficacy Analyses in Subgroups in RA Studies*

- a) *Does the FDA agree with the choice of ACR 20 at Week 24?*
- b) *Does the FDA agree with the variables and subgroup definitions selected for the pooled analyses?*

**FDA Response:**

You propose to conduct subgroup analyses for the pre-specified primary statistical analyses of the primary efficacy endpoint for each of the five Phase 3 studies (i.e., 3 RA, 1 PsA, and 1 AS study). This proposal is acceptable, as are your subgroup definitions for age and sex. However, for the subgroup analyses by race, we recommend you use subgroups defined in the 2005 *Collection of Race and Ethnicity Data in Clinical Trials Guidance*: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White, as well as Hispanic or Latino and Not Hispanic or Latino. If ethnicity data or racial data were not collected in such detail, then your proposed subgroup definitions are acceptable for your efficacy analyses by race.

**You propose to conduct your subgroup analysis for body weight by quartiles for each of the individual studies. We agree with your proposal. However, if there is a marked difference between weight quartiles, a more detailed analysis may be warranted, e.g., by weight deciles.**

**You also propose to pool all three Phase 3 RA studies to conduct subgroup efficacy analyses (i.e., by age, gender, race, and weight) by three treatment groups (i.e., placebo and two golimumab groups). However, your proposed analyses would pool heterogeneous treatment groups and RA populations (e.g., MTX-naive, inadequate response to MTX, and prior use of anti-TNF therapy) who may exhibit disparate efficacy responses. Therefore, we recommend you submit subgroup analyses maintained by study and treatment group for the RA studies.**

*Question 6 - Impact of Study Agent Supply Shortage on Efficacy*

*Does the FDA agree that the criteria (3 or more consecutive missing doses) selected for the conduct of this sensitivity analysis is appropriate?*

**FDA Response:**

**You propose to perform sensitivity analyses for the golimumab- and MTX-monotherapy groups by excluding patients who missed  $\geq 3$  weekly oral doses of MTX for the pre-specified primary efficacy endpoints in Studies 5 and 6 (i.e., ACR50 at Week 24 and ACR20 at Week 14, respectively). We agree that the criteria for missing MTX (i.e.,  $\geq 3$  weekly consecutive oral doses of MTX) is appropriate because RA patients who miss  $\leq 2$  consecutive doses of MTX would not be expected to flare.**

**In Studies 5 and 6, since both oral MTX and SC golimumab doses were missed and the primary statistical comparison is between the combination golimumab/MTX groups and the MTX monotherapy group, perform sensitivity analyses on the primary endpoints by excluding patients who missed  $\geq 3$  weekly oral doses of MTX or missed  $\geq 1$  SC dose of golimumab. In Studies 8, 9, and 11, since SC golimumab doses were missed, perform sensitivity analyses on the pre-specified primary statistical analysis for the primary endpoints by excluding patients who missed  $\geq 1$  SC dose of golimumab.**

**For each of the five Phase 3 studies, provide sensitivity analyses for the primary efficacy analyses in which all patients who missed administrations (i.e.,  $\geq 3$  weekly consecutive oral doses of MTX or  $\geq 1$  SC dose of golimumab) due to the shortage are classified as non-responders for the primary efficacy endpoints. Additional sensitivity analyses may be requested after the extent of the shortage is considered.**

**Provide counts of all patients who missed any study treatments due to the shortage, by study and treatment group, and how many administrations were missed. Also identify any data points which were missed and whether any imputation method was applied for these data.**

**Provide datasets identifying subjects who missed any administrations due to the shortage and how many were missed. Also indicate missing data points due to the shortage.**

## DISCUSSION

The Sponsor stated that the reasons patients missed study medications (e.g., supply issues, patient non-compliance) were not collected in the five Phase 3 trials. Therefore, the Division's specific requested analyses cannot be performed. The Sponsor proposed to conduct the Division's requested analyses for all patients who missed study medication including patients who missed due to supply issues, non-compliance, or other reasons. Dr. Meaker recommended that the Sponsor perform all of the Division's requested analyses for patients who missed study medication only during the timeframe of the MTX and golimumab shortage (e.g., November 2006 to February 2007). The Sponsor agreed to submit Dr. Meaker's requested analyses in the initial BLA submission.

The Sponsor asked if the statistical analysis plans (SAPs) for the Phase 3 trials need to be amended to include the requested Division's analyses. Dr. Meaker stated that since the study medication shortages were unexpected, the SAPs do not need modification.

### *Question 7 - Overall Plans for Evaluating Safety*

*Does the agency agree with the proposed integration of the safety data as described including table formats? Specifically does the Agency agree that the following safety analyses are appropriate to adequately evaluate the safety profile of golimumab in the proposed indications:*

- *Safety analyses through Week 16 (common minimum placebo-controlled period) by dose and indication (3 RA studies pooled, and each PsA and AS study) as the primary focus of the safety evaluation*
- *Selected safety analyses by dose of golimumab through Week 16, through Week 24, and through the last safety cutoff date prior to filing on pooled data across all 5 Phase 3 studies in the 3 rheumatologic indications*
- *Analyses of malignancies and serious infections on pooled data across all Phase 2b and 3 studies including the 5 Phase 3 studies, the Phase 2 RA study, and the Phase 2 study in severe asthma*
- *Analyses of malignancies on pooled data across all studies (with and without healthy volunteer studies)*
- *Listings of all Serious Adverse Events (SAEs) that occurred in ongoing studies up to a safety cutoff date approximately 6 months prior to the BLA submission*

### **FDA Response:**

**You propose to perform multiple analyses to evaluate the safety of the following:**

1. **golimumab monotherapy, combination golimumab/MTX therapy, and combination golimumab/other DMARD therapy for RA**

2. golimumab monotherapy and combination golimumab/MTX therapy for PsA
3. golimumab monotherapy for AS

#### RA Indication

You propose the following as the “primary focus of the safety evaluation” for the RA indication:

“pool all three Phase 3 RA studies; evaluate safety up to Week 16; and pool several distinct treatment groups assigned by randomization into three groups (i.e., placebo and two golimumab groups).”

We have the following concerns regarding these proposed safety analyses:

1. The Week 16 cut-off does not represent the longest exposure to the assigned treatment during the controlled phases of the studies.
2. The analyses pool three heterogeneous RA populations (i.e., MTX-naïve, inadequate response to MTX, and prior use of anti-TNF therapy) that may have different susceptibilities to adverse reactions.
3. The proposed analyses would not maintain distinctions between assigned treatment groups, which could impede the evaluation of the tolerability and safety of the use of golimumab with concomitant MTX [Study C0524T05 (Study 5) and Study C0524T06 (Study 6)] and/or other DMARDs [C0524T11 (Study 11)]. Even where two treatment groups in different studies may appear identical, pooling could be problematic. For example, in Studies 5 and 6, the golimumab100 & MTX combination treatment groups are different because in Study 6 RA patients are only receiving one new therapy (golimumab100); whereas, in Study 5, RA patients are receiving two new therapies (golimumab100 and MTX).

See the 2005 *Premarketing Risk Assessment Guidance* and the 2005 *Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review* Guidance for further details regarding pooling of data for the safety evaluation.

To address these concerns we recommend instead that you include the following safety analyses:

1. For the three RA studies, provide individual study safety results analyzed by assigned treatment group from randomization with safety evaluation up to 16 weeks.
2. For the three RA studies, provide individual study safety results analyzed by assigned treatment group from randomization with safety evaluation up to 24 weeks, excluding patients who entered early escape (EE). For Study 5, provide safety results analyzed by assigned treatment group from randomization with safety evaluation up to 52 weeks (or cut-off date at the time of the original BLA submission), excluding patients who entered EE.
3. For the three RA studies, provide individual study safety results analyzed for the patients who entered EE for the duration of the escape period (e.g., for Study 6, Week 16 to Week 52 or up to the cut-off date at the time of the original BLA submission) by

rescue therapy [e.g., in Study 6, analyze by the four rescue therapies (1 golimumab50 & MTX group and 3 golimumab100 & MTX groups)].

4. For the proposed pooled analyses of the three Phase 3 RA studies, we recommend you extend the analyses of safety up to Week 24 excluding the EE patients. Furthermore, with these analyses, you should provide the percentage of patients by the three treatment groups who were on stable doses of concomitant MTX, sulfasalazine, hydroxychloroquine, and/or steroids at baseline and who received additional MTX during the treatment period.

#### PsA and AS Indications

You propose to analyze the Week 16 data for the PsA and AS studies for the PsA and AS indications, respectively. This is acceptable. However, we recommend for each study you also analyze the safety results by assigned treatment at randomization up to 24 weeks, excluding patients who entered EE. Patients who enter EE can be analyzed separately by rescue therapy group from Weeks 16 to 24.

#### Pooled Rheumatologic Indications

You propose to pool the five Phase 3 rheumatologic studies and analyze safety data by three groups (i.e., placebo, golimumab 50, and golimumab 100) at Week 16, Week 24, and at the safety cut-off date. This is acceptable. However, we also recommend you conduct additional pooled analyses of safety data (including Malignancies and Infectious SAEs) from the five Phase 3 studies at Week 24 (excluding the EE patients). For these analyses, provide the percentage of patients by the three treatment groups who were on stable doses of concomitant MTX, sulfasalazine, hydroxychloroquine, and/or steroids at baseline and who received additional MTX during the treatment period.

#### Malignancies and Infectious SAEs

You propose to conduct analyses of malignancies and Infectious SAEs by pooling data from the five Phase 3 studies, the one-year Phase 2 RA study, and the one-year Phase 2 asthma study. Your proposal is acceptable. Additionally, see our recommendations for additional analyses for malignancies and Infectious SAEs under "Pooled Rheumatologic Indications" and our response to Question 12.

You propose to include narratives of all deaths and all discontinuations leading to adverse events (DAEs). Depending on the frequency and type of SAEs noted, we may ask you to include narratives and case report forms of SAEs.

## DISCUSSION

The Sponsor and the Division discussed safety analyses and presentations proposed by the Sponsor and the Division to evaluate the safety of the golimumab in the RA, PsA, and AS indications. The Sponsor attempted to clarify the Division's requested safety analyses for the five individual Phase 3 studies, the three pooled RA studies, and the five pooled Phase 3 studies by providing examples of mock-up safety tables. Discussions between Dr. Brodsky and the Sponsor focused on appropriate cut-off time points for the safety analyses and how to

incorporate and display the data of patients who enter early escape in the safety analyses. Dr. Brodsky agreed with the Sponsor that all golimumab safety analyses should be conducted on treated patients (not all randomized patients) according to treatment actually received. The Sponsor stated that they will submit a summary of their understanding of the Division's requested safety analyses based on the Division's comments in the draft responses and the subsequent discussion during the Pre-BLA Meeting. The Division agreed to review the Sponsor's submission and to provide a response to the Sponsor's proposals in the Post Meeting Comments..

Additionally, the Sponsor has provided a test submission in CDISC/SDTM format for review by Dr. Rochester's group. Data provided in this format will allow for additional analyses to be performed by the Agency.

#### POST MEETING COMMENTS

We have reviewed your August 29, 2007 submission which summarizes your understanding of our requested safety analyses. Based on this submission, we believe further clarification of our requested analyses is necessary and is provided in the following comments and tables.

You may submit the safety analyses proposed in the pre-BLA meeting package to support the safety of golimumab for the three proposed indications (i.e., RA, PsA, and AS) in your initial BLA submission. However, also provide the following safety analyses (Studies C0524T02, C0524T03, C0524T05, C0524T06, C0524T08, C0524T09, and C0524T11 are referred to as Studies 2, 3, 5, 6, 8, 9, and 11, respectively):

- 1) Individual study safety results from Week 0 up to Week 24 for Study 5 (see Table 1); for Study 6 (see Table 3); for Studies 9 and 11 (see Table 4), and for Study 8 (see Table 5).
- 2) Individual study safety results for Study 5 from Week 0 up to Week 52 (if patients have not reached Week 52, then include exposure up to the last cut-off date). Provide this analysis in your initial BLA submission and in the Safety Update (see Table 2).
- 3) Pooled analyses of the three RA studies (Studies 5, 6, and 11) from Week 0 up to Week 24. See Table 6.
- 4) Pooled analyses of the five Phase 3 studies (Studies 5, 6, 8, 9, and 11) from Week 0 up to Week 24. See Table 7.

For all of the above analyses provide:

- 1) Deaths, nonfatal SAEs, adverse events leading to discontinuation (DAEs), adverse events (AEs), related AEs, and possible TNF inhibitor associated AEs (all and serious infections, all malignancies, all and serious hypersensitivity reactions, all and serious hepatotoxicity, all and serious neurologic events, all congestive heart failure, all autoimmunity syndromes, immunogenicity, and all injection site reactions).
- 2) Central tendency, outlier, and marked outlier analyses for laboratory data, vital signs, and QTc data. Include analyses for leukopenia, neutropenia, thrombocytopenia, and pancytopenia.

In addition, provide pooled analyses of malignancies and serious infections in the seven Phase 2 and Phase 3 studies — the two Phase 2 studies [Study 2 (RA) and Study 3 (asthma)] and the five Phase 3 studies (Studies 5, 6, 8, 9, and 11). Provide these analyses in your initial BLA submission and in the Safety Update (see Table 8) and include comparison with expected rates of malignancy based on the Surveillance, Epidemiology, and End Results (SEER) database.

For the pooled RA study analyses (#3) and the pooled rheumatologic study analyses (#4) it is acceptable to provide baseline MTX, sulfasalazine, and hydroxychloroquine use by pooled treatment group (as you displayed in Table 8 of your August 29, 2007 submission). In addition, provide the number and percentage of patients who initiated MTX therapy during the treatment period by pooled treatment group (e.g., only patients in Study 5 initiated MTX therapy during the treatment period; in contrast, patients in Studies 6 and 11 who received MTX during the treatment period received baseline MTX).

For the key time points and exposures in Study 5 refer to Table I and for the key time points and exposures in Studies 6, 8, 9, and 11 refer to Table II.

In all of the tables, if the treatment groups have different exposures to study medication, provide the rate of AEs (e.g., number of treated patients with  $\geq 1$  AE per person years).

**Table I: Key Time Points and Exposures for Study 5**

Week	0	24	28	52
Patients who do not escape	A	B	C	G
Patients who escape	D	E	F	H

A + B represent the W0-W28 exposure of patients who do not escape  
 C represents the W28-W52 exposure of patients who do not escape  
 D + E represent the W0-W28 exposure of patients who escape  
 F represents the W28-W52 exposure of patients who escape  
 G + H represent exposure of patients after W52

**Table II: Key Time Points and Exposures for Studies 6, 8, 9, and 11**

Week	0	16	24	52
Patients who do not escape	a	b	f	h
Patients who escape	c	d	g	i

a represents the W0-W16 exposure of patients who do not escape  
 b represents the W16-W24 exposure of patients who do not escape  
 c represents the W0-W16 exposure of patients who escape  
 d represents the W16-W24 exposure of patients who escape  
 f, g, h, and i represent exposure of patients after W24

**Table 1: Representative AE Table for Study 5 from W0 up to W24<sup>1</sup>**

	Treatment groups assigned by randomization			
	MTX	Golimumab100	Golimumab50 & MTX	Golimumab100 & MTX
Treated Patients with ≥ 1 AE, n (%)	A + D	A + D	A + D	A + D

<sup>1</sup> This table does not include AEs that occurred after W24 (it does not include data from B, C, E, F, G, or H). Since W24 occurs prior to the start of the escape period (W28), there are no columns for rescue therapy. This table includes only patients who received ≥ 1 dose of study medication.

**Table 2: Representative AE Table for Study 5 from W0 up to W52<sup>1</sup>**

	Treatment groups assigned by randomization				Rescue Therapies	
	MTX	Golimumab100	Golimumab50 & MTX	Golimumab100 & MTX	Golimumab50 & MTX	Golimumab100 & MTX
Treated Patients with ≥ 1 AE, n (%)	A, B, C, D, + E	A, B, C, D, + E	A, B, C, D, + E	A, B, C, D, + E	F	F

<sup>1</sup> This table does not include AEs that occurred after W52 (it does not include data from G or H). This table includes only patients who received ≥ 1 dose of study medication. If patients have not reached Week 52, then include exposure up to the last cut-off date in your initial BLA submission and in your Safety Update.

**Table 3: Representative AE Table for Study 6 from W0 up to W24<sup>1</sup>**

	Treatment groups assigned by randomization				Rescue Therapies	
	Stable MTX <sup>2</sup>	Golimumab100	Golimumab50 & stable MTX	Golimumab100 & stable MTX	Golimumab50 & MTX	Golimumab100 & MTX
Treated Patients with ≥ 1 AE, n (%)	a, b, + c	a, b, + c	a, b, + c	a, b, + c	d	d

<sup>1</sup> This table does not include AEs that occurred after Week 24 (it does not include data from f, g, h, or i). This table includes only patients who received ≥ 1 dose of study medication.

<sup>2</sup> In this treatment group, patients will be exposed to stable MTX during W0-W24. After W24, these patients will crossover to another treatment.

**Table 4: Representative AE Table for Individual Studies 9 and 11 from W0 up to W24<sup>1</sup>**

	Treatment groups assigned by randomization			Rescue Therapies	
	Placebo ± DMARDs	Golimumab50 ± DMARDs	Golimumab100 ± DMARDs	Golimumab50 ± DMARDs	Golimumab100 ± DMARDs
Treated Patients with ≥ 1 AE, n (%)	a, b, + c	a, b, + c	a, b, + c	d	d

<sup>1</sup> This table does not include AEs that occurred after W24 (it does not include data from f, g, h, or i). This table includes only patients who received ≥ 1 dose of study medication.

**Table 5: Representative AE Table for Study 8 from W0 up to W24<sup>1</sup>**

	Treatment groups						Rescue Therapies	
	Placebo ±MTX		Golimumab50 ±MTX		Golimumab100 ±MTX		Golimumab50± MTX	Golimumab100± MTX
	- MTX	+ MTX	- MTX <sup>2</sup>	+ MTX <sup>3</sup>	- MTX <sup>2</sup>	+ MTX <sup>3</sup>		
Treated Patients with ≥1 AE, n (%)	a, b, +c	a, b, +c	a, b, +c	a, b, +c	a, b, +c	a, b, +c	d	d

1 This table does not include AEs that occurred after W24 (it does not include data from f, g, h, or i). This table includes only patients who received ≥ 1 dose of study medication.

2 Golimumab monotherapy treatment groups

3 Golimumab/MTX treatment groups

**Table 6: Representative AE Table for the Three Pooled RA Studies (Studies 5, 6, and 11) from W0 up to W24<sup>1</sup>**

	Pooled Treatment Groups <sup>2</sup>			Rescue Therapies	
	Placebo ±DMARDs	Golimumab50 ±DMARDs	Golimumab100 ±DMARDs	Golimumab50± DMARDs	Golimumab100± DMARDs
Treated Patients with ≥1 AE, n (%)	a, b, c, A, +D	a, b, c, A, +D	a, b, c, A, +D	d	d

1 This table does not include AEs that occurred after W24 (it does not include data from f, g, h, or i from Study 6 and Study 11 and it does not include data from B, C, E, F, G, or H from Study 5). This table includes only patients who received ≥ 1 dose of study medication.

2 Pooling eleven treatment groups from Studies 5, 6, and 11 into three treatment groups

**Table 7: Representative AE Table for the Five Pooled Phase 3 Studies (Studies 5, 6, 8, 9, and 11) from W0 up to W24<sup>1</sup>**

	Pooled Treatment Groups <sup>2</sup>			Rescue Therapies	
	Placebo ±DMARDs	Golimumab50 ±DMARDs	Golimumab100 ±DMARDs	Golimumab50± DMARDs	Golimumab100± DMARDs
Treated Patients with ≥1 AE, n (%)	a, b, c, A, +D	a, b, c, A, +D	a, b, c, A, +D	d	d

1 This table does not include AEs that occurred after W24 (it does not include data from f, g, h, or i from Studies 6, 8, 9, and 11 and it does not include data from B, C, E, F, G, or H from Study 5). This table includes only patients who received ≥ 1 dose of study medication.

2 Pooling multiple treatment groups from Studies 5, 6, 8, 9, and 11 into three treatment groups

**Table 8: Representative Malignancy and Serious Infections Table for the Seven Pooled Phase 2 and Phase 3 Studies (Studies 2, 3, 5, 6, 8, 9, and 11) <sup>1</sup>**

	Pooled Treatment Groups <sup>2</sup>	
	Placebo ± DMARDs	Golimumab ± DMARDs
Treated Patients with ≥ 1 AE, n (%)	a, b, c, A, D, I, + J	a, b, c, A, D, I, + J
Rate of AEs (number of treated patients with ≥ 1 AE per person-year at risk)	a, b, c, A, D, I, + J	a, b, c, A, D, I, + J

<sup>1</sup> For Study 2, the time frame is from W0 up to W20 (because at W20 several groups crossover to different treatments); for Studies 6, 8, 9, and 11 the time frame is from W0 up to W24; and for Studies 3 and 5 the time frame is from W0 up to W52 (or if Week 52 was not reached at cut off). This table includes only patients who received ≥ 1 dose of study medication.

<sup>2</sup> Pooling multiple treatment groups from Studies 2, 3, 5, 6, 8, 9, and 11 into two treatment groups (placebo ± DMARDs and golimumab ± DMARDs).

I represents exposure in Study 2 from W0 to W20 and J represents exposure in Study 3 from W0 to W52.

*Question 8 - Safety of Golimumab Monotherapy Versus Combination Therapy*

*Does the agency agree that the planned safety displays are appropriate for comparing the safety of golimumab monotherapy with the safety of the golimumab/MTX combination in RA and PsA?*

**FDA Response:**

See our responses to Question 7 for our recommendations for the comparing the safety of all the treatment groups in the three proposed indications.

**DISCUSSION**

The Division stated that their requested safety analyses will assess the safety of the golimumab monotherapy and the golimumab combination therapy groups and no additional analyses are recommended at this time.

**POST MEETING COMMENTS**

Although no additional analyses were requested at the pre-BLA meeting, in order to enable assessment of the safety of golimumab as monotherapy and as combination therapy in PsA, submit an analysis of safety subgrouped by concomitant MTX use in Study 8 (see Table 5, above).

*Question 9 - Content of Modules 2.7.4 and 5.3.5.3*

*In accordance with FDA Guidance for Industry on Submitting Marketing Applications According to the ICH-CTD Format (August 2001), Centocor proposes to provide a comprehensive safety analysis within Module 2.7.4 with supportive documentation and additional integrated analyses in Module 5.3.5.3. Does the Agency agree with Centocor's planned approach to Module 2.7.4 and 5.3.5.3?*

**FDA Response:**

**You propose to include the most important safety analyses and the interpretation of these analyses in Module 2.7.4 (Summary of Clinical Safety) and include all the datasets and supportive documentation in Module 5.3.5.3 [Reports of Analyses of Data from More than One Study (Including Any Formal Integrated Analyses, Meta-Analyses, and Bridging Analyses)]. This is acceptable. Refer to the June 2007 *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document Draft Guidance* for further details regarding the appropriate content for Modules 2.7.4 and 5.3.5.3 in your BLA submission.**

**For your comments regarding the "primary safety displays" see our response to Question 7.**

*Question 10 - Subject Exposure*

*Does the FDA agree with the proposed approach for summarizing exposure data and the proposed durations of exposure categories?*

**FDA Response:**

**You propose to summarize cumulative exposure and duration of exposure to golimumab by dose (i.e., 50 mg and 100 mg) for the rheumatologic indications by including all five Phase 3 studies through Week 16, Week 24, and the last safety data cut-off. Your proposal is acceptable. However, also include a summary of cumulative exposure and duration-of-exposure to golimumab by dose for the rheumatologic indications including all five Phase 3 studies through Week 24, excluding patients who entered the EE phase.**

**In addition, you should consider including the exposure of two combination treatment groups (i.e., MTX & golimumab 50 mg every 4 weeks and MTX & golimumab 100 mg every 4 weeks) from Study 2 (the RA Phase 2 study) to your exposure tables for the following reasons:**

- 1. These two combination dose regimens in Study 2 were identical to two of the dose regimens in the Phase 3 RA studies.**
- 2. Patients in Study 2 had a significant duration-of-exposure to the treatment regimens (i.e., 52 weeks).**

3. **Study 2 appears to target a similar population (patients with an inadequate response to MTX) as one of the phase 3 RA studies (i.e., Study 6).**

**You proposal to define the duration-of-exposure to SC golimumab as the time interval between the first and the last dose of golimumab received plus four additional weeks is acceptable.**

*Question 11 - Subgroup Analyses*

- *Does the agency agree with the proposed variables and subgroup definitions for the safety analyses?*
- *Does the agency agree that the proposed displays are appropriate for evaluating the safety of golimumab in the specific subgroups?*

**FDA Response:**

**You propose subgroup definitions for age (< 65, ≥ 65, and ≥ 75), gender (male, female), and baseline weight (by quartiles). These subgroup variables and definitions are acceptable. For racial and ethnicity subgroup definitions, see our response to Question 5.**

**Refer to our concerns expressed in Question 7 regarding your proposal to pool safety data from the three RA studies.**

*Question 12 - 120-Day Safety Update*

*Does the FDA agree that the proposal for updating the golimumab safety experience in the 120-day Safety Update Report is adequate?*

**FDA Response:**

**For the Safety Update, you propose to include new safety data from approximately six months of additional dosing in the five ongoing Phase 3 studies and to pool data by three treatment groups (e.g., placebo, golimumab50, and golimumab100) from the 3 RA studies, 1 PsA study, and 1 AS study. Your proposal is acceptable.**

**Since Study 5 has one-year, blinded, controlled data, we recommend you include updated safety analyses of Study 5 from Week 0 to Week 52 by treatment group assigned by randomization, excluding patients who entered EE.**

**POST MEETING COMMENTS**

Question 12 was not discussed in the pre-BLA meeting, but further clarification of the requested analyses for the Safety Update is addressed in the post meeting comments for Question 7 and 15.

*Question 13 - Format of Analysis Datasets*

*Does the FDA agree with Centocor's approach to providing SAS datasets and programs?*

**FDA Response:**

**The planned approach is acceptable.**

*Question 14 - Test SDTM datasets*

*Does the Agency agree with this approach? If so, whom should Centocor contact if a follow-up is needed?*

**FDA Response:**

**The planned approach is acceptable.**

*Question 15 - Container Closure Comparability*

*Does the agency agree that the following biochemical comparability data for the Liquid in Vial (LiV) and Pre-Filled Syringe (PFS), and a bioequivalence trial comparing the LiV used in Phase 3 trials with the Centocor auto-injector, will be sufficient to support the registration of the PFS and the auto-injector as the to-be-marketed presentations of golimumab?*

**FDA Response:**

**You propose to support the registration of two commercial presentations of golimumab (PFS with either the [REDACTED] or the Centocor auto-injector) with comparability data, safety and immunogenicity results of Study C0524T24 [a single-dose bioequivalence study of golimumab (LiV given by syringe/needle and the Centocor auto-injector)]; and the safety/efficacy results of the LiV given by syringe/needle in the five Phase 3 studies. You also state that the PFS (with the [REDACTED] or the Centocor auto-injector) was not administered in the five Phase 3 clinical studies. Since the PFS delivery system may have greater immunogenicity than the LiV given by syringe/needle because of increased aggregates, it is essential that you evaluate the safety and immunogenicity of the PFS delivery system compared with the LiV given by syringe/needle after multiple-dose testing prior to marketing either PFS delivery system. Since the LiV presentation of golimumab was used in all your Phase 3 studies, the current extent of data is presently acceptable to support only the submission of the LiV formulation in your BLA.**

**b(4)**

The comparability plan appears adequate, but should address potential differences in immunogenicity of the two presentations and ease-of-use of the two PFS presentations.

Describe how the rates of immunogenicity of chronic dosing with the two presentations (LiV and PFS) were measured and compared. Given the higher levels of subvisible particles in the PFS drug product, data regarding the rate of immunogenicity of chronic dosing with the PFS presentation should be present in the initial BLA submission.

Describe in more detail how ease-of-use of the two PFS syringe presentations (auto-injector [redacted] was addressed. Indicate the number of patients studied and, of these, the percentage with significant arthritis in the hands. In your BLA submission, include information on any manual dexterity limitations that would preclude the use of the [redacted] or the Centocor auto-injector in the relevant patient populations. Detailed ease-of-use and formal human-factors study information should be present in the initial BLA submission. Clarify if a formal human-factors study has been performed.

b(4)

Additional CMC Comments:

1. Regarding the final formulation, you state that concentrations of histidine and sorbitol in Phase 3 clinical and validation batches of CNTO 148 final bulk were [redacted] than initially intended (i.e. 5.6 mM and 4.1%, respectively vs. [redacted]). You state that this probably occurred during the final [redacted]. These phenomenons are likely to be difficult to control during manufacturing. Please clarify if:
  - a) this was the concentration for all nine clinical and validation batches, or are they average values. Provide the standard deviation for these values.
  - b) 5.6 mM and 4.1% will be the permanent formulation concentration for these two excipients
  - c) how you intend to control levels of histidine and sorbitol, given the [redacted]
2. For GMPs pertaining to manufacture of combination devices, please refer to the FDA Guidance "Current Good Manufacturing Practice for Combination Products" (Draft 2004) <http://www.fda.gov/oc/combination/OCLove1dft.pdf>. This Guidance document identifies considerations that may be relevant for pre-approval inspections for the combination devices.
3. [redacted]
4. Please consider bundling some or all of the [redacted] protocols that you intend to submit to the CNTO148 BLA. Follow-ups to [redacted] reprocessing protocols should be submitted to the product annual report, not as CBEs.

b(4)

b(4)

b(4)

5. **Please submit actual chromatograms from stopper and other elastomer extraction studies. Peaks on the chromatograms should be identified to the extent feasible.**
6. **The accuracy of the proposed DW-SE-HPLC should be confirmed with another orthologous method such as analytical ultracentrifugation.**

**DISCUSSION:**

The Sponsor asked the Division to clarify what data they were referring to when discussing increased aggregates in relation to the container closure comparability. Dr. Brorson explained that the answer referred to the five to ten fold increased level of sub-visible particles in the prefilled syringe (PFS) as compared to the liquid-in-vial (LiV). The Sponsor explained that they believe these particles are largely  droplets. Additionally, the Sponsor noted that, in a preliminary analysis, the levels of subvisible particles are only two-fold higher in the PFS compared to placebo. Dr. Brorson stated that sub-visible particles are still a concern as  droplets often associate with proteins and can form protein  complexes. The Sponsor stated that the two presentations (PFS and LiV) are comparable biochemically in all other assays in the comparability exercise. Dr. Swann stated that there is still a concern with the subvisible particles because the absence of protein in the particles cannot be confirmed.

b(4)

Dr. Brorson stated that clinical data is required in the BLA to address the potential for increased immunogenicity of the PFS presentation compared to the LiV presentation used in the five Phase 3 trials. The Sponsor asked if the clinical data requirement (due to a change in biologic product presentation) was a new Agency requirement. Dr. Brorson stated that this is not a new requirement and that the Agency has required clinical immunogenicity and safety data to support approval of new formulations/presentations of biologic products for many years. The Sponsor asked if submission of clinical data was necessary to support the PFS presentation of golimumab given that the immunogenicity profiles of three approved TNF inhibitors are well-known. Dr. Siegel stated that the approved TNF inhibitors have different rates of immunogenicity and hypersensitivity reactions and that these rates cannot be predicted for a new TNF inhibitor and therefore clinical data will be required. The Sponsor asked if results do not demonstrate a relationship between immunogenicity and the efficacy and safety of golimumab given by the LiV formulation whether it would be reasonable to assume immunogenicity would also not affect efficacy or safety of golimumab given by PFS. Dr. Siegel and Dr. Brorson reiterated that clinical data are required to demonstrate that differences between the presentations will not result in clinically meaningful differences in immunogenicity and safety.

Dr. Brorson stated that the above clinical data requirements could be met by submitting subgroup analyses of the ongoing Phase 3 trials and a new clinical trial may not be required to assess the immunogenicity of the PFS presentation. Data may be obtained by an analysis of existing trials if both the LiV and PFS presentations were used.

The Sponsor proposed to provide data from ongoing Phase 3 trials in which patients started treatment with LiV, and were switched to PFS. According to the Sponsor, there will be safety and immunogenicity data from about 250 RA, PsA, and AS patients who received greater than one SC injection of golimumab from the PFS presentation at the time of the Safety Update (120 days into the review period of the BLA). The Sponsor proposed submitting these data with an

evaluation of immunogenicity rates as well as injection site and hypersensitivity reactions in the Safety Update. Dr. Brodsky explained that the Division expects the analyses to include multiple-dose exposures given that product immunogenicity can increase over time. Dr. Siegel stated that given the Sponsor's proposal to submit the immunogenicity data in the Safety Update, it appears that this information will not be submitted in the initial BLA submission. According to the 2005 *Good Review Management Principles and Practices for PDUFA Products* Guidance, the initial BLA submission should contain all the data needed to support the entire application including all the proposed to-be-marketed presentations. Dr. Rappaport re-emphasized that immunogenicity data supporting the PFS presentation should be submitted in the original BLA to reduce the possible need for multiple cycle reviews and that there is no guarantee that the Division will be able to review data submitted in the Safety Update to support approval of the PFS delivery system. Therefore, if additional information required to support approval is submitted in the Safety Update, then it is at the Sponsor's risk.

The Sponsor will provide the Division with a written proposal regarding data the Sponsor will submit in the initial BLA to support the approval of the PFS presentation. The Sponsor stated they will include information on the number of patients who had the following: received multiple doses of the PFS presentation, had assessments for injection site reactions and hypersensitivity reactions, and/or developed an immunogenic response.

The Sponsor clarified that they have completed ease-of-use studies for the auto injector device. The [redacted] syringe is an approved 510k device and has been tested as mandated by the CDRH guidance, but not on a golimumab-specific basis. The Sponsor questioned whether referencing the 510k application was possible and if these data are sufficient. Dr. Love explained that the [redacted] is cleared as a general use product; therefore, the completed study under the 510(k) may not address the issues of the golimumab treatment population. The Sponsor questioned whether studies in impairment are necessary for both devices since patients would have a choice between the two. Dr. Love further clarified that the application should contain information on whether patients in the three rheumatologic indications will be able to use these two devices. These study results are also important for preparing labeling and instructions for use. These data could be provided by submitting the information the Sponsor presently has, cross referencing the 510(k), and justifying why the 510(k) studies would be acceptable for use in indicated rheumatologic populations. However, whether these data would be adequate would be determined upon review of the data. A focused study in rheumatologic patients may be necessary.

b(4)

The Sponsor stated that in the interest of saving time at the meeting, they will address the additional CMC comments in a written follow-up submission.



*Question 16 – eCTD Format*

*Does the review team anticipate the need to have documents or files provided in alternate formats?*

**FDA Response:**

**No, we do not anticipate the need to have documents or files provided in alternative formats.**

*Question 17 – Electronic Submission Pathway*

*Are there any specific concerns that Centocor should anticipate regarding submission of the eCTD via the FDA Gateway?*

**FDA Response:**

**For all questions regarding submission of the eCTD, we recommend you go to <http://www.fda.gov/cder/regulatory/ersr/ectd.htm> or e-mail [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov).**

**Additional Comments:**

**1) In your April 2007 SAP for Study 6, you propose the following three tiered testing for the first co-primary efficacy endpoint (i.e., the proportion of patients who achieve an ACR20 response at Week 14):**

- a) The primary statistical comparison (for superiority) will be between the low- and high-dose combination groups (i.e., golimumab 50 & MTX and golimumab 100 & MTX, respectively) with the MTX monotherapy group.**
- b) If this is significant then a comparison (for superiority) between the low-dose combination group with MTX and a comparison (for superiority) between the high-dose combination group with MTX will be performed.**
- c) If “positive test results for the analysis” above is achieved, then a comparison (for superiority) between the golimumab and MTX monotherapy groups will be performed.**

**However, you did not specify what “analysis” needs to be positive prior to performing the third analysis. If the high-dose combination with MTX comparison (one of your secondary analyses) is positive, then it would be acceptable to perform the third analysis. However, if the high-dose combination with MTX comparison is negative, then it would not be acceptable to perform the third analysis under your tiered SAP.**

**2) For Study 5, clarify whether patients who received MTX (i.e., Groups I, III, and IV) received MTX until the 52-database lock (pages 42-43 of the protocol state that patients**

- will receive MTX until the 52-database lock; however, page 21 of protocol states that patients will receive MTX until Week 48).
- 3) **Submit a MedDRA “coding dictionary” – a list of all investigator verbatim terms and the preferred terms to which they were mapped – that includes bidirectional coding (i.e., from verbatim term to preferred term and from preferred term to verbatim term).**
  - 4) **For all five Phase 3 studies, submit SAEs, discontinuations leading to adverse events (DAEs), and most frequent adverse events for the following levels of MedDRA hierarchy: the primary-system organ class (SOC), the secondary-system organ class (SOC2), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lowest-level term (LLT).**
  - 5) **Submit information on product medication errors in your BLA application.**
  - 6) **Provide a comprehensive list of patients with potentially clinically significant laboratory, vital sign, or EKG abnormalities.**
  - 7) **In your ISS, discuss the safety profile of golimumab with regard to known TNF inhibitor-associated, significant adverse reactions.**
  - 8) **In your BLA submission, provide the following information and the location of this information (see the 2004 Clinical Review Template MAPP 6010.3 for more details):**
    - **Section 2.6 Other Relevant Background Information- important regulatory actions in other countries or important information contained in foreign labeling**
    - **Section 4.6 Financial Disclosures - financial arrangements with clinical investigators as recommended by the 2001 *Financial Disclosure by Clinical Investigators* Guidance**
    - **Section 5.3 Exposure-Response Relationships - important exposure-response assessments**
    - **Section 7.1.7.3.1 - Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.**
    - **Section 7.1.7.3.2 - Laboratory Analyses focused on outliers or shifts from normal to abnormal). Also provide the criteria used to identify outliers.**
    - **Section 7.1.7.3.3 - Marked outliers and dropouts for laboratory abnormalities.**
    - **Section 7.1.8.3.1 - Analysis of vital signs focused on measures of central tendencies.**
    - **Section 7.1.8.3.2 -Analysis of vital signs focused on outliers or shifts from normal to abnormal.**
    - **Section 7.1.8.3.3 -Marked outliers for vital signs and dropouts for vital sign abnormalities.**
    - **Section 7.1.9.3.1 - QTc or other significant EKG analyses focused on measures of central tendency**
    - **Section 7.1.9.3.2 - QTc or other significant EKG analyses focused on outliers or shifts from normal to abnormal**

- **Section 7.1.9.3.3 - QTc or other significant EKG marked outliers and dropouts for QTc or ECG abnormalities**
- **Section 7.1.14 Human Reproduction and Pregnancy Data - information on golimumab exposure in pregnant women**
- **Section 7.1.16 Overdose Experience - overdose experience with golimumab in humans, including signs and symptoms of patients who received an overdose of golimumab.**
- **Section 7.4.2.1 - Explorations for dose dependency for adverse findings**
- **Section 7.4.2.2 - Explorations for time dependency for adverse findings**
- **Section 7.4.2.3 - Explorations for drug-demographic interactions**
- **Section 7.4.2.4 - Explorations for drug-disease interactions**
- **Section 7.4.2.5 - Explorations for drug-drug interactions**
- **Section 8.2 - Dosing considerations for important drug-drug interactions**
- **Section 8.3 - Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.**

**Comments from the Office of Surveillance and Epidemiology (OSE):**

The following general comments provided by OSE at the time of pre-BLA meetings are offered for your consideration:

1. If you and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then you are encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP). If you plan to submit a RiskMAP with the original submission, please remember to submit all planned materials identified within the RiskMAP that will be necessary to implement your proposal.
2. For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:
  - a) **Premarketing Risk Assessment:**  
<http://www.fda.gov/cder/guidance/6357fnl.htm>
  - b) **Development and Use of Risk Minimization Action Plans:**  
<http://www.fda.gov/cder/guidance/6358fnl.htm>
  - c) **Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:** <http://www.fda.gov/cder/guidance/6359OCC.htm>

- 3. If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA/BLA application.**
- 4. You are encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.**

Linked Applications	Sponsor Name	Drug Name
IND 12729	CENTOCOR INC	CNTO 148 (golimumab)
IND 12723	CENTOCOR INC	Golimumab (Human Monoclonal Antibody to Tumor Necrosis Factor Alpha, rTNV148B, CNTO 148)
IND 9925	CENTOCOR INC	Golimumab (Human Monoclonal Antibody to Tumor Necrosis Factor Alpha, rTNV148B, CNTO 148)

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/s/

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LISA MALANDRO  
09/21/2007

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20852

Our Reference: pre-IND

MAY 19 2005

Centocor, Incorporated  
Attention: Bethany Paxson  
Director, Worldwide Regulatory Affairs  
200 Great Valley Parkway  
Malvern, PA 19355-1307

Dear Ms. Paxson:

Please refer to your **pre-Investigational New Drug Application (IND)** for "Golimumab," and to the telephone conversation held on April 21, 2005, between representatives of your firm and this agency. As requested in your letter of February 18, 2005, a copy of our memorandum of that meeting (or telephone conversation) is attached for your information.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective Oct. 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, Maryland 20852

If you have any questions, please contact me at (301) 827-4358.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Cristi L. Stark".

Cristi L. Stark, MS  
Regulatory Project Manager  
Division of Review Management and Policy  
Office of Drug Evaluation VI  
Center for Drug Evaluation and Research

Enclosure: Meeting Summary



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Biologics Evaluation and Research

Memorandum

Date: **MAY 19 2005**  
From: *Cristi Stark, DRMP, ODEVI, HFD-109*  
To: Pre-IND Centocor, Incorporated  
Subject: Type B Teleconference Summary

Teleconference Date: March 21, 2005

Time: 2:30pm-3:30pm

Location: WOC2, Conference Room H

Meeting Requestor/Sponsor: Centocor, Incorporated

Product: Golimumab (CNTO 148)

Proposed Use: Treatment of Psoriatic Arthritis (PsA)

Type of meeting: Pre-IND, Pre-Phase 3

Meeting Purpose: To discuss the proposed Phase 3 clinical plans for CNTO 148 to support an indication in psoriatic arthritis (PsA).

FDA Attendees: Elektra Papadopoulos, MD, Medical Officer, DTBIMP/ODEVI  
Jeffrey Siegel, MD, Medical Team Leader, DTBIMP/ODEVI  
Cristi Stark, MS, Regulatory Project Manager, DRMP/ODEVI  
Marc Walton, MD, PhD, Division Director, DTBIMP/ODEVI  
Bo-Guang Zhen, PhD, Biostatistics Team Leader, BTSS/OPaSS

Sponsor Attendees: Dan Baker, MD, Executive Director, Clinical R&D  
Mohan Bala, PhD, Director, Outcomes Research  
Anna Beutler, MD, Director, Clinical R&D  
Michael Elliott, MD, PhD, Senior Vice President, Clinical R&D  
John Han, PhD, Associate Director, Biostatistics  
Ben Hsu, MD, Associate Director, Clinical R&D  
Michael Mack, PhD, Assistant Director, Biostatistics  
Bethany Paxson, Director, Worldwide Regulatory Affairs  
Linda Vega, Manager, Worldwide Regulatory Affairs

Honghui Zhou, PhD, Director, Clinical Pharmacokinetics, Clinical Pharmacology

**Background:** Golimumab is a fully human monoclonal antibody to TNF $\alpha$ . It binds TNF $\alpha$  2-4 fold greater than infliximab. Centocor proposes to submit (6) Phase 3 trials to support licensure for rheumatoid arthritis (RA), PsA and ankylosing spondylitis (AS). The BLA will contain 24-week data to support a claim for the

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This meeting will focus on golimumab for the treatment of PsA. Study C0524T08 is a multicenter, randomized, double-blind, placebo-controlled, 3-arm trial of golimumab administered subcutaneously every 4 weeks in subjects with active PsA who have had an inadequate response to current or previous DMARD or NSAID therapy.

#### **FDA comments:**

As agreed during our March 8, 2005 End of Phase 2 meeting for RA, only one clinical trial is needed for PsA.

As agreed during the April 19, 2005 pre-IND/pre-Phase 3 teleconference for ankylosing spondylitis, Centocor will assess all study subjects for the potential effect of golimumab on response to vaccination.

#### **Sponsor questions and FDA response:**

1. *The doses of golimumab selected for evaluation in the Phase 3 program for the PsA disease indication are:*

- 50mg injected subcutaneously (SC) every 4 weeks
- 100mg SC every 4 weeks

*Data supporting the safety and pharmacokinetics of these doses have been collected from preclinical pharmacology studies in cynomolgus monkeys and from human clinical studies with golimumab in subjects with rheumatoid arthritis.*

*Does the FDA agree with our rationale for the choice of proposed dose and schedule for the Phase 3 program?*

Although the review division agrees in principle with the rationale for the selection of the above doses, they are fixed doses, and we therefore have concerns regarding both the efficacy and safety of the product when it is administered to patients at either end of the weight spectrum. Please be aware that you will need to include in the product's licensing application an analysis of safety and efficacy in patients subdivided by weight, and that this

information must have sufficient sensitivity to ensure that there are not important differences in safety or efficacy related to weight.

2. *The proposed trial in PsA includes the following subject population:*

- *Subjects with active PsA and psoriasis (at least 3 tender and 3 swollen joints and psoriasis skin lesion at least 2 cm in diameter) despite current or previous DMARD or NSAID therapy. DMARD therapy is defined as taking a DMARD for at least 3 months, or DMARD intolerance. NSAID therapy is defined as taking a NSAID for at least 4 weeks.*
- *Concomitant MTX is permitted but not required in the study. Subjects will be stratified at randomization by baseline MTX use. DMARDs other than MTX will not be allowed.*
- *It is expected that approximately 50% of study subjects in each arm will be treated with a combination of study drug and MTX, and 50% of subjects will receive a study drug without MTX.*

*Does the Agency agree that the population selected for this trial will be supportive for the proposed indication of \_\_\_\_\_ subjects with active psoriatic arthritis (PsA)?*

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*Yes, population selected for this trial will be supportive for the proposed indication of \_\_\_\_\_ subjects with active PsA.*

3. *Protocol C0524T08 is planning to enroll 330 subjects, and the 2 co-primary endpoints (tested sequentially) in the trial are the proportion of subjects with an ACR20 response measured at week 14, and the change in baseline in total radiographic scores of the hands and feet at week 24 (the maintenance of benefit will also be assessed at week 52). The major secondary endpoints for C0524T08 are:*

- *Proportion of subjects with an ACR20 response at week 24 to demonstrate maintenance of benefit*
- *Proportion of subjects achieving Psoriatic Arthritis Response criteria (PsARC) at week 14*
- *Proportion of subjects with  $\geq 75\%$  improvement in Psoriasis Area Severity Index (PASI) at week 14*
- *Change from baseline in HAQ measured at Week 24 (maintenance of benefit will be assessed at Week 104)*

*Does the FDA agree that the choice of endpoints and timing of the endpoint assessments are appropriate to support the proposed indications? Specifically, does the Agency agree that the size of the trial, the patient population, and the endpoints chosen will be sufficient to support an indication that includes \_\_\_\_\_*

b(4)

*subjects with active psoriatic arthritis?*

\_\_\_\_\_

b(4)

\_\_\_\_\_ it need not be designated as a major secondary endpoint as the ACR20 is now well-accepted as an outcome measure for PsA.

4. *The C0524T08 protocol has the following pre-defined early escape criteria: subjects with < 10% improvement in both tender and swollen joints at week 16 will enter early escape with golimumab treatment. Centocor estimates that about 50% of the placebo subjects and about 10% of the golimumab treated subjects will qualify for early escape. For the week 24 analyses, subjects entering early escape will be considered as non-responders for ACR20.*

*All subjects will have radiographs taken at Week 0. Subjects entering early escape will have radiographs taken at the time of early escape at week 16. Subjects not entering early escape will have radiographs taken at week 24.*

*The co-primary analysis for the inhibition of progression of structural damage will be based on the change from baseline in total radiographic scores of the hands and feet at week 24. Week 24 radiographic scores for subjects who entered early escape will be derived from linear extrapolation using week 0 and 16 timepoints.*

*Does the FDA agree with the analysis methods chosen for this trial?*

FDA expressed concern about the validity of linear extrapolation of radiographic data from week 16 to week 24. We recommend you add sensitivity analyses to assess the effect of the use of linear extrapolation as you propose for patients entering early escape. In particular, we recommend you include an analysis of radiographic progression from week 0 to week 24 for all patients as randomized.

Centocor asked for clarification on the last statement. Currently only the placebo subjects entering early escape will have x-rays at week 16 and extrapolated to week 24. All other subjects will have films at week 24. Centocor stated that they have no plans for collecting films at both week 16 and week 24 on all subjects and expressed the concern that to do so may be exposing subjects to too many x-rays.

Centocor inquired if they could use an alternative approach where they would perform x-rays on all patients at week 24, rather than using linear extrapolation from week 16 to week

24 in placebo subjects entering early escape. Using this approach, placebo subjects entering early escape would only have x-rays at baseline and at week 24 film, not at week 16. All the subjects would be analyzed according to their originally assigned treatment group. Placebo subjects entering early escape would, thus, have had some exposure to infliximab by the time of the week 24 x-ray and would still be analyzed with the other placebo subjects who did not enter early escape.

FDA stated this is acceptable but noted that this is a risk to Centocor. There is a possibility of underestimating the treatment effect.

5.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

b(4)

6. *For all trials, randomizations will be stratified by site and for some studies by another factor (i.e., prior medications, laboratory value, or disease severity) as well. Since sites may be enrolling only a few subjects, it will be difficult to ensure balanced treatment assignments within each stratum by using a traditional block randomization schedule. Centocor plans on using an adaptive stratified randomization method in both trials. Additionally, analyses will not include site as a factor because of the small number of subjects expected per center.*  
***Does the Agency agree with this approach?***

This approach may be reasonable but is dependent on the details of the adaptive stratified randomization method, which have not been supplied to FDA as of yet.

7. *In the primary endpoint analysis of each 3-arm study, the two dose groups of golimumab will be combined, and then compared to placebo. If this combined comparison is significant, then each dose group will be compared to placebo separately. A Type I error*

*of 0.05 will be used for all of these tests.*

***Does the Agency agree with this approach?***

This approach is adequate for controlling the inflation of type I error rate. However, it is unclear which hypothesis test result you will use to propose a claim of efficacy. We recommend that a claim be made only based on a comparison between each individual dose group vs. placebo, not on the combined comparison. In addition, we are concerned that this decision rule has the following potential risks that should be recognized:

- If the null hypothesis is not rejected in the test for the combined groups, then it is not permissible to continue, even if an informal assessment suggests that one of the dose groups vs. placebo comparisons is significant.
- If the null hypothesis is rejected in the test for the combined groups, there still may be no significance between any of the dose groups vs. placebo in the following tests.
- The proposed method of pooling the two dose groups in the test may reduce the statistical power, in the event that one of the dose groups is similar to or worse than the placebo in the endpoint to be tested.

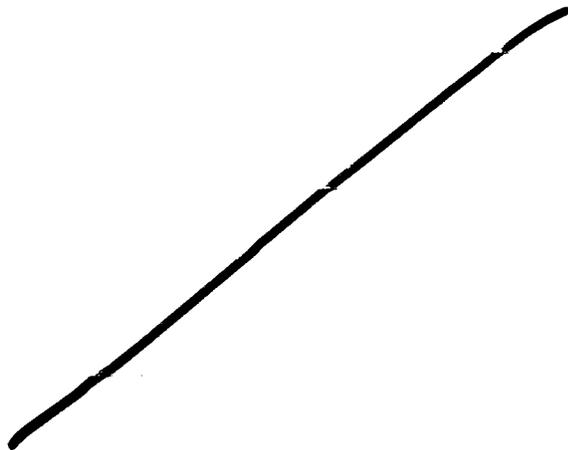
8. *Centocor intends to file a single BLA for golimumab in 3 indications: rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA). It is Centocor's intention to pool the safety information from all three indications and submit the initial BLA with 24-week data from all 6 trials. The clinical package will be composed of the following studies:*
- a. *A Phase 1 single ascending dose IV study in rheumatoid arthritis subjects (C0466T01)*
  - b. *A Phase 1 single and multiple ascending dose SC study in rheumatoid arthritis subjects (C0466T02)*
  - c. *A Phase 2 dose-ranging SC study in rheumatoid arthritis subjects (C0524T02)*
  - d. *24-week data from 2 Phase 3 studies in rheumatoid arthritis subjects (C0524T05 & C0524T06)*
  - e. *24-week data from 1 Phase 3 study in psoriatic arthritis subjects (C0524T08)*
  - f. *24-week data from 1 Phase 3 study in ankylosing spondylitis subjects (C0524T09)*

*At the time of the initial BLA, the estimated safety database from all three rheumatologic indications will include greater than 1600 subjects treated for 6 months and ~500 treated for one year. At the time of the submission of the 120-day safety update, it is estimated that the majority of the subjects will have completed one year of treatment and the file will be supplemented with this information.*

***Does the Agency agree that the proposed safety database is adequate to support registration in all three indications?***

In principal this database may be sufficient for product labeling if the adverse event profile is similar to that seen with other TNF blocking agents. However, the final decision would depend upon the observed safety profile. If new unexpected safety signals are detected, additional safety data may be required.

9.



b(4)



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Biologics Evaluation and Research

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Memorandum

Date: **MAY 17 2005**  
From: *Cristi Stark, DRMP, ODEVI, HFD-109*  
To: IND 9925  
Subject: Type B Meeting Summary

---

Teleconference Date: April 21, 2005

Time: 3:30pm – 5:00pm

Location: WOC2, Conference Room I

Meeting Requestor/Sponsor: Centocor, Incorporated

Product: Golimumab (CNTO 148)

Proposed Use: Treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis

Type of meeting: End of Phase 2

Meeting Purpose: To discuss the proposed Phase 3 CMC development plans for CNTO 148 to support indications for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

**FDA Attendees:**

Kurt Brorson, PhD, Product Reviewer, DMA/OBP  
Jason Lipman, Consult Device Reviewer, GHDB/CDRH  
Rosemarie Neuner, MD, Medical Reviewer, DTBIMP/ODEVI  
Archana Reddy, MS, Regulatory Project Manager, OBP/OPS  
Jeff Siegel, MD, Medical Team Leader, DTBIMP/ODEVI  
Pandu Soprey, Consult Device Reviewer, GHDB/CDRH  
Cristi Stark, MS, Regulatory Project Manager, DRMP/ODEVI  
Anthony Watson, Consult Device Team Leader, GHDB/CDRH

**Sponsor Attendees:**

**Background:** Golimumab is a fully human monoclonal antibody to TNF $\alpha$ . It binds TNF $\alpha$  2-4 fold greater than infliximab. Centocor proposes to submit (6) Phase 3 trials to support licensure for RA, psoriatic arthritis (PsA) and ankylosing spondylitis (AS). The initial BLA will contain 24-week data to support a claim for the

b(4)

function. This meeting will focus on golimumab CMC and device issues.

**Sponsor questions and FDA response:**

1. *Does FDA agree with the proposed plan for demonstrating comparability between Phase 2 and Phase 3 clinical material?*
  - *Assuming that the biochemical and biological characterization studies support product comparability and the described monkey PK study demonstrates comparability within the proposed margin for AUC (0-10day) and Cmax, does FDA concur with Centocor's proposal to use the new liquid formulation of CNTO 148 in the upcoming Phase 3 clinical studies?*

Overall the proposed plan for demonstrating comparability between the Phase 2 and Phase 3 clinical material appears acceptable. Please note that in Table 6 on page 16, your particulate matter (visible and subvisible, USP/EP) states a specification of reporting a result (for subvisible particles \_\_\_\_\_). This needs to be changed to an exact specification for both translucent and subvisible particles and not a reporting result. In addition, please add a tests and specification for content uniformity of the filled syringes or justify non-applicability of this testing.

b(4)

Centocor stated that it is their original intent that translucent material and subvisible will be reported as a result during the IND phase. Centocor believes that for a subcutaneous product, exact specifications for translucent material and subvisible are not required by the USP. Currently there is not a history with the new formulation, so it is difficult to set specifications at this point in development. Once a data set is established, Centocor intends to decide whether an exact specification if needed. Regarding the uniformity of dose, this is a liquid. Both tests, extractable volume and water volume in container, will have a specification.

FDA stated that reporting is acceptable in clinical trials for subvisible and translucent materials; however, when the BLA is submitted, an exact specification is needed. This is a protein product: particulate matter and aggregates can cause immunogenicity; FDA expects testing and specifications. USP requirements are not applicable in this situation. FDA concurs with Centocor's approach to uniformity of dose.

2. *Does FDA agree with the process validation plan for the qualification of validation batches?*

The pooling strategy described on page 23 is acceptable as long as all intermediates that are pooled meet in process acceptance criteria. It should be noted that the pooling strategy can result in risk of blending good harvests and/or [REDACTED] with intermediates with unexpected or unanticipated process issues. b(4)

It appears that the Phase 3 syringes will be hand filled at the Centocor lab in PA and subsequent fillings at the Cilag facility. Please provide more detail on what this means. Where will the validation batches be made (the validation should be performed at Cilag)? How many conformance lots will be made at Cilag?

Centocor stated that the [REDACTED] syringes were only prepared to perform comparability studies (they were not used in clinical studies). All Phase 3 syringes will be made and validated at Cilag in their [REDACTED]. There will be a total of 3 conformance lots made. b(4)

3. *Does FDA agree with the proposed content for information to be filed in an IND amendment and subsequently in a BLA as a combination product for approval of a pre-filled safety auto injector device for product launch?*

In general this appears acceptable. However, please address the following comments/recommendations:

- You state that the acceptance criteria for the deliverable volume is  $\geq$  Label claim. The standard dose range for doses greater than 0.2mL is  $\pm 5\%$  with a 95% confidence interval. Please specify the accuracy of the deliverable volume.
- Your pre-filled syringe appears to contain an air bubble. Please address the risk of subcutaneous emphysema that may occur as a result of the air bubble in the pre-filled syringe.
- We recommend that you add a terminal fill mark to the device.

Centocor stated that they fully expect to meet or exceed the safety standards for the acceptance criteria for deliverable volume. The volume will either deliver 0.5mL or 1.0mL. Measuring accuracy will be in place before use in clinical trials. The current air bubble in the demo is larger due to [REDACTED] filling; however, all devices in the market have a small air bubble (all devices used in clinical trials will have a smaller air bubble). Centocor believes that the air bubble helps the user see the presence of the drug and poses a minimal risk of subcutaneous emphysema. They will validate the risk in tolerability and bioequivalent studies. Regarding the terminal fill mark, this may be technically challenging. The project team will evaluate the fill mark as recommended by FDA. b(4)

April 21, 2005

**FDA comments/questions:**

1. Has                      been inspected by FDA? If so, when?

**b(4)**

                     was inspected January 22 - 26, 2001. A 483 was issued with 6 minor observations noted.

2. Is there a DMF or 510K for the autoinjector?

Currently there is neither a DMF or 510K. Centocor does not intend for the device to stand alone. They asked if a DMF could be a mechanism to file the technical info.

FDA stated that a 510K submission will make it easier for CDRH to review and for CDER to refer to the device.

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On Original**

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RA 2005048797

FOOD AND DRUG ADMINISTRATION  
 CENTER FOR DRUG EVALUATION AND RESEARCH  
 OFFICE OF NEW DRUGS  
 OFFICE OF DRUG EVALUATION VI  
 DIVISION OF REVIEW MANAGEMENT AND POLICY

Woodmont Office Complex II, 6<sup>th</sup> Floor  
 1451 Rockville Pike  
 Rockville, Maryland 20852-1448  
 FAX #: 301-827-5397

FACSIMILE TRANSMISSION RECORD

TOTAL NUMBER OF PAGES: 13 (Including Cover Page)

FAX TO: ~~Patricia~~ Bethany Paxson / Centocor, Inc.

Facsimile Telephone No. 610-651-6123 Voice Telephone No. 601-651-6979

FROM: Cristi Stank / FDA / CDER / DRMP

Facsimile Telephone No. ~~301-827-5397~~ Voice Telephone No. ~~301-827-5397~~

DATE: 4/6/05 TIME: 3:50 pm

MESSAGE:  
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## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20852

Our Reference: BB-IND 9925

APR 06 2005

Centocor, Incorporated  
Attention: Bethany Paxson  
Director, Worldwide Regulatory Affairs  
200 Great Valley Parkway  
Malvern, PA 19355

Dear Ms. Paxson:

Please refer to your **Investigational New Drug Application (IND)** for "Golimumab" and to the meeting held on March 8, 2005, between representatives of your firm and this agency. As requested in your letter of January 10, 2005, a copy of our memorandum of that meeting is attached for your information.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions. Effective Oct. 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, Maryland 20852

If you have any questions, please contact me at (301) 827-4358.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Cristi L. Stark".

Cristi L. Stark, MS  
Regulatory Project Manager  
Division of Review Management and Policy  
Office of Drug Evaluation VI  
Center for Drug Evaluation and Research

Enclosure: Meeting Summary



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Biologics Evaluation and Research

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Memorandum

**Date:** APR 22 2004  
**From:** Cristi Stark, DRMP, HFM - 589  
**To:** IND 9925  
**Subject:** Type C Teleconference Summary

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**Teleconference Date:** March 25, 2004

**Time:** 2:00-3:00pm

**Location:** WOC2, Conference Room H

**Meeting Requestor/Sponsor:** Centocor, Incorporated

**Product:** Human Monoclonal Antibody (rTNV148B, CNTO 148) to Tumor Necrosis Factor Alpha

**Proposed Use:** Treatment of rheumatoid arthritis

**Type of meeting:** Other-preliminary plans

**Meeting Purpose:** To obtain feedback regarding the acceptability of the proposed clinical development plan for CNTO 148 as it relates to the proposed indications for RA, AS, and PsA.

**Sponsor questions and FDA response:**

1. *Does the Agency agree with our proposal to support indications in rheumatoid arthritis (RA) with pooled safety data from all 3 related populations?*

FDA agrees with your proposal for pooled safety data under the reasoning that you will submit all three indications simultaneously in the BLA. The pathophysiology of RA, ankylosing spondilitis (AS), and psoriatic arthritis (PsA) are similar. Subjects are frequently taking similar concomitant DMARDs. Data from existing anti-TNF agents have similar safety profiles in each of these diseases.

Centocor responded that it is their intention to file all safety and efficacy data in the BLA.

2. *Are the size of the planned safety database and the plan to submit this data adequate to support approval for the indication \_\_\_\_\_ s of RA?*

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Yes. There are adequate numbers of subjects for each indication (RA=1150, AS=300, and PsA=420) given that the numbers are similar to those of trials of previously approved agents for these diseases and given that the mechanism of action for CNTO 148 should be similar to already approved anti-TNF drugs. Similarly, an adequate number of subjects will be exposed to CNTO 148 to determine safety. However, this is dependent on the results of the efficacy and safety data generated from the clinical trials.

3. *Assuming positive results in all trials described, indications will also be sought for AS and PsA. Would the Agency accept one BLA for all three indications?*

Yes.

Centocor then inquired the current requirements in the event they choose to submit RA alone.

FDA responded that for RA alone approximately 1000-1500 patients treated for a year at the recommended dose or higher would be sufficient. However, this also depends on what is seen in the data.

4. *Does the Agency have any comments on the proposed study designs, including the following parameters?*

For the most part the proposed study design is acceptable, however please see the comments for the following parameters:

- a. *Subject population (inclusion/exclusion criteria)*

Subjects in the RA trial who have an inadequate response to MTX should have failed a minimum dose of 15mg/week rather than the stated 10mg/week, or those subjects intolerant of MTX $\geq$ 15mg/week. Also include congestive heart failure (CHF) to the list of exclusion criteria.

Centocor agreed.

- b. *Sample sizes*

The sample sizes are appropriate.

- c. *Treatment regimens (range of doses and frequency of administration)*

CNTO 148 is too early in development for FDA to give concurrence on the proposed dosing based on the lack of evidence for efficacy, especially since the inherent risks of the expected TNF inhibition (e.g., immunosuppression) may manifest at a lower dose than what is efficacious. Additionally, at the currently proposed maximal dosing of CNTO 148 every 4 weeks you expect approximately 25% of subjects to have trough levels below 1µg/mL, which based on your posthoc analysis of infliximab, may be subtherapeutic. Have you considered adding a higher dose than 100mg every 4 weeks or increasing the frequency of dosing? We will withhold further comment until the Phase 2 data has been analyzed and submitted.

The CNTO 148 trial in MTX-Naïve subjects with RA will administer CNTO 148 every 4 weeks that will result in ~50% of subjects with lower trough levels than those that are associated with sustained clinical activity (based on infliximab data). To overcome the potential ethical problem of leaving subjects inadequately treated on either placebo (MTX alone) or MTX plus CNTO 148 50mg every 4 weeks; you could consider adding additional DMARDs (e.g., SSZ, except anti-TNF drugs) to the treatment regimen after 24 weeks as rescue therapy for patients with an inadequate response. This would allow for additional therapy for signs and symptoms while allowing for the acquisition of 52-week X-ray data on CNTO 148. So long as more subjects in the placebo arm received rescue DMARDs, this would be conservative (any effect this would have on X-ray erosions would decrease the estimate of the drug effect of CNTO 148 for the 12-month assessments). However, it should also be noted that if unexpectedly more subjects in the CNTO 148 arm took rescue DMARDs this would represent a confounding variable.

Centocor responded that their trough levels vary from 0.1 through a higher range. They did agree that it was too early to pick a dose; instead the chosen doses are merely placeholders. Once the safety data is in they will re-evaluate the chosen dose, as 50mg/week may not be appropriate.

FDA reminded Centocor that the ethical problems may be overcome with the addition of additional DMARDs (not anti-TNF) for treatment in the extra weeks as rescue therapy.

Centocor agreed to take this point under consideration.

*d. Primary efficacy endpoints and major secondary endpoints*

The primary endpoints are sufficient, however; as discussed below, FDA requires 6-month data for each of the indications (i.e., PsA). Additionally, except for the RA study you have not indicated the collection of X-rays rather than the MRI data presumable ~~\_\_\_\_\_~~ Since MRI has not been validated FDA would like to know if these MRI data would be intended for a

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labeling claim or just as exploratory analyses.

FDA also recommends enrolling patients with all subtypes of PsA into the PsA trials to better capture a representative sample of the PsA population and to make the results of the trials more generalizable. Similarly, including patients with AS associated with psoriasis or inflammatory bowel disease would make the results of the AS trials more generalizable.

Centocor replied that unless things change, they would not use MRI data. Also they understood FDA's point about including all subtypes of patients with PsA into the trial but they would still need a large number of tender joint scores.

FDA stated that it might be worthwhile to consider lowering the numbers of scores needed. Infliximab had good data with only three.

5. *Two studies are planned for each indication. For RA and AS, 1 of 2 studies will include a 6-month primary endpoint and use an active comparator. The second of the 2 trials in RA and AS, and both PsA trials will be placebo-controlled and include a primary endpoint at week 14, after which all patients can receive active treatment. Does the Agency agree with the assessment of the primary endpoint at week 14 in placebo-controlled trials of RA, AS, and PsA patients who have active disease despite continued treatment with standard therapies?*

Currently FDA expects blinded 6-month data for approval of these 3 indications; however, given the difficulty with IRB committees regarding undertreating subjects and that the efficacy of this class of drugs is well studied, we would accept additional data from a double-blind, randomized withdrawal study of responsive PsA and [2<sup>nd</sup> study] RA subjects following 24 weeks. This would provide supportive data demonstrating long-term efficacy of CNTO 148 in PsA and RA.

Centocor then asked for clarification. Does this mean that they can have 1 trial for 6 months and then a second as a randomized withdrawal trial?

FDA replied that the second trial could have a 3-month endpoint. A possibility would be to keep treating patients on CNTO 148 (blinded or open-label) for 6 months and then randomly withdrawal responders and look at the percentage of these patients that flare. If the placebo arm has a larger number of flares, this will show the drug is still effective.

Centocor responded that this proposal was far more complex than what they were considering. Instead they thought after the first study to run a second 6-month blinded study and allow for escape.

FDA stated this idea was fine except that the understanding was that the IRB would not approve another study over 3 months.

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Centocor and FDA then agreed to table this issue and discuss it in future meetings.

6. *Does the Agency have any comments on the proposed plan to introduce a liquid formulation into the clinical program to support initial marketing with that formulation?*

At this time it is premature to discuss the structure of a clinical study, which incorporates aspects of comparability testing outside the context of a discussion concerning CMC. Also what is the relationship between the 200 and 250 patients in the study? What percentage of patients will gain experience with the new formulation compared to the total in the study?

Centocor stated that there are a total of 250 subjects in the RA study of which, at the time of the BLA submission, 200 will be exposed to the syringe and the other 50 to placebo injection. In answer to the second question, 250 subjects out of a total of 1000 will have gained experience with the new formulation. The first RA study will be completely liquid while the second RA study will be a stand-alone with the 250 subjects receiving the new formulation.

FDA then recommended that Centocor perform analytical ultra-centrifugation studies for a demonstration that aggregate levels don't change. Also with the new formulation, has the manufacturing process remained unchanged?

Centocor replied that the manufacturing is unchanged with the excipient and the components remaining the same. The only difference is a slight change in the dose and pH. Centocor then added that in addition to the pre-filled syringe, they are also exploring an auto-injecting device.

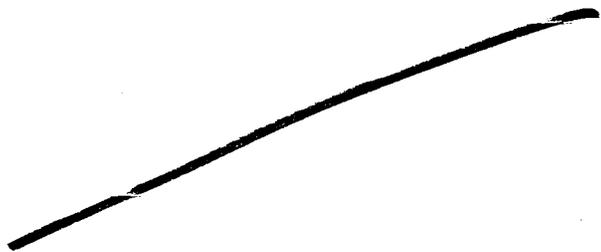
FDA informed Centocor that an auto-injecting device is viewed as a far different manner than the pre-filled syringe. For the auto-injecting device Centocor will need to perform more testing (pharmacokinetics is needed at a minimum). Consider an 80-125 comparability interval with a reasonable number of subjects. Also check to make sure the immunogenicity is the same by ultra-centrifugation and stability studies.

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b(4)

**FDA Attendees:** Kurt Brorson, OPS/DMA  
Martin Green, ODEVI/DTBIMP  
Keith Hull, ODEVI/DTBIMP  
Jeff Siegel, ODEVI/DTBIMP  
Joel Schiffenbauer, ODEVI/DAADDP  
Cristi Stark, ODEVI/DRMP  
Marc Walton, ODEVI/DTBIMP  
Carolyn Yancey, ODEVI/DAADDP  
Bo-guang Zhen, OPaSS/BTSS

**Sponsor Attendees:** Daniel Baker, M.D, Executive Director, Immunology Clinical  
Research & Development  
Anna Beutler, M.D., Associate Director, Immunology Clinical  
Research & Development  
Kimberly DeWoody, Ph.D., Director, Biostatistics  
Michael Elliott, M.D., Ph.D., Vice President, Immunology Clinical  
Research & Development  
Jody Ann Gould, Ph.D., Director, Worldwide Regulatory Affairs  
Martin Graham, Ph.D., Director, Pharmacokinetics, Clinical  
Pharmacology  
John Han, Ph.D., Associate Director, Biostatistics  
Stella Jones, Ph.D., Vice President, Worldwide Regulatory Affairs  
Susan Lee, Manager, Worldwide Regulatory Affairs  
Karen Nelson, Manager, Worldwide Regulatory Affairs  
Mahboob Rahman, M.D., Ph.D., Associate Director, Immunology  
Clinical Research & Development  
James Tiede, Ph.D., Vice President, Clincial Operations  
Jianping Zhang, Ph.D., Research Fellow, Pharmacokinetics, Clinical  
Pharmacology



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DEPARTMENT OF HEALTH & HUMAN SERVICES

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CTS-CRS-USA-C0524T  
Public Health Service  
2004009348

Food and Drug Administration  
Rockville, MD 20852

Our Reference: BB-IND 9925

APR 22 2004

Centocor, Incorporated  
Attention: Stella Jones, PhD  
Vice President, Worldwide Regulatory Affairs  
200 Great Valley Parkway  
Malvern, PA 19355

Dear Dr. Jones:

Please refer to your **Investigational New Drug Application (IND)** for "Human Monoclonal Antibody (rTNV148B, CNTO 148) to Tumor Necrosis Factor Alpha", and to the telephone conversation held on March 25, 2004, between representatives of your firm and this agency. As requested in your letter of January 20, 2004, a copy of our memorandum of that telephone conversation is attached for your information.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see <http://www.fda.gov/cber/transfer/transfer.htm> and <http://www.fda.gov/OHRMS/DOCKETS/98fr/03-16242.html>. Until further notice, however, all correspondence regarding this IND should continue to be addressed to:

CBER Document Control Center  
Attn: Office of Therapeutics Research and Review  
HFM-99, Room 200N  
1401 Rockville Pike  
Rockville, Maryland 20852-1448

If you have any questions, please contact me at (301) 827-4358.

Sincerely yours,

Cristi L. Stark, MS  
Regulatory Project Manager  
Division of Review Management and Policy  
Office of Drug Evaluation VI  
Office of New Drugs  
Center for Drug Evaluation and Research

Enclosure: Meeting Summary



**Food and Drug Administration**  
Center for Biologics Evaluation and Research

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Memorandum

**Date:** June 13, 2001  
*LOT*

**From:** Lori A. Tull, Regulatory Project Manager  
OTRR/DARP, HFM-588

**To:** Centocor, Incorporated, and CBER participants

**Subject:** Pre-IND Teleconference  
Centocor, Incorporated  
Human anti-TNF $\alpha$  monoclonal antibody (rTNV148B)

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**Teleconference Date: May 14, 2001**

**SPECIFIC QUESTIONS AND DISCUSSION**

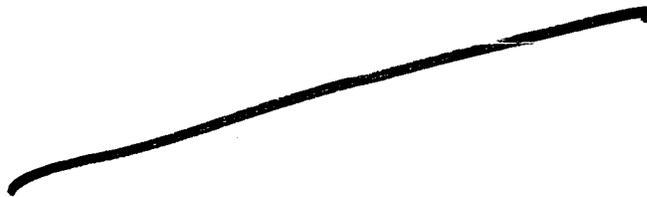
**Toxicology Program**

1. Our toxicology program has been previously discussed with Agency representatives. Due to limited availability of study agent, one month of toxicology data will be available in the initial IND. A 3-month study to support dosing of rTNV148B for greater than one month is scheduled to begin in August 2001. Since 6 months of toxicity data is available on our analogous anti-mouse TNF $\alpha$  monoclonal antibody (cV1q), does the Agency agree with the proposed plan to submit one month of data in the IND in support of the initial (single-dose) Phase 1 trial?
  - This would be supportive data for a single-dose trial for IV administration. This would not be supportive for SQ administration. Because a SQ study has not been completed at this time, the potential for development of antibodies with this route of administration is unknown. This data will be critical in determining how to proceed to the clinical studies. If no antibodies are found to develop in a SQ administration toxicology study, the data will be supportive for a SQ administration clinical study. If antibodies are found to develop in the SQ

administration toxicology study, the sponsor will need to look at alternative toxicology studies in an appropriate animal model.

- Centocor commented that they were planning a 3 month IV toxicology study to support the SQ administration. The agency replied that we prefer to see experience with both routes of administration. In addition to the above comments, there is potential for different injection site reactions and a difference in bioavailability that would be unknown without a SQ toxicology study.

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3. The clinical program for rTNV148B includes studies in pediatric patients. Because studies of infliximab and other anti-TNF agents have not revealed any unique toxicity in the pediatric population, no toxicology studies are planned to evaluate the effects of rTNV148B in immature animals. Does the Agency agree with this approach?

- The agency suggested that Centocor wait to proceed with pediatric studies until seeing results from the adult studies. Additional animal studies that reflect the pediatric population may be needed.

4. Does the agency agree that the 1-month intravenous dose toxicity study in monkeys supports up to 4 weekly subcutaneous clinical doses of rTNV148B?

- It is not the agency's preference to use IV data to support a SQ study. This could result in a need for additional nonclinical data for phase 2/3 studies.

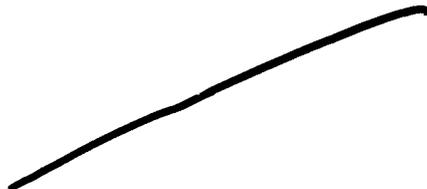
#### **Phase 1 Studies in Rheumatoid Arthritis**

5. Does the Agency agree that the initial Phase 1 study can be conducted in the RA population, as defined in the study synopsis, and that the proposed number of patients and follow-up period are satisfactory?

- The agency agreed with this proposal.

6. Are the planned doses and the time(s) between cohorts for the first-in-human Phase 1 study acceptable?
  - The agency is concerned that there may be unexpected safety concerns at the higher dose levels since they are as yet unexplored with analogous molecules. For the higher doses in Group 3, there should be a 1 week follow up before moving up to the next dose.
  - Centocor agreed to adjust the follow-up time accordingly.
7. Does the Agency concur with the proposed stopping rules for the initial Phase 1 (intravenous administration) study?
  - Stopping rules should be added for grades 3 and 4 adverse events.
8. The proposed patient RA population may require Phase 1 studies to be conducted at multiple sites. Does the Agency agree that two to three sites per study may be used?
  - The agency agreed to this proposal.
9. Based upon the toxicology data that will be available (6 months IV dosing study of cV1q in mice; 3 months IV dosing study of rTNV148B, single subcutaneous dose and 1 month multiple subcutaneous dose pharmacokinetic studies, and injection site irritation studies in monkeys), the Phase 1/2 multi-dose study of subcutaneous rTNV148B may include 3 to 6 months of treatment with active drug. Does the Agency agree that the toxicology data will support clinical dosing for 3 to 6 months?
  - This will depend on the actual results of the studies. The agency commented that the applicability of homologous models depends on equivalence factors.

**Overall Clinical Development Program**



b(4)

Product Discussion

14. Please submit the V<sub>H</sub> and V<sub>L</sub> sequences of the antibody to the IND.
- Centocor agreed to submit this information.
15. Why is the karyology of the mAb producing cell line human? Wasn't the cell substrate a mouse myeloma cell?
- Centocor didn't know why Table 1 listed the karyology of the cell bank as human. They said that a mouse myeloma cell line was used as the transfection substrate. The Agency said that if the cell were human in origin, there would be additional testing requirements. Centocor said that they would double check the karyology.
15. Do you plan on making an MCB and WCB? What is the timeframe for this?
- Centocor currently has a [redacted] research cell bank. They plan to eventually designate this as the MCB and then develop a WCB.
17. Is the [redacted] facility?
- [redacted]
18. Please provide a list with sources of all animal derived materials and their country of origin, including amino acids, tween 80, etc.
- Centocor agreed to submit this information.
19. CBER encourages you to switch to [redacted]
- Centocor replied that they are working hard to make the switch to [redacted]. Their intent is to complete the switch before phase 2, and said that it will definitely be done before phase 3.
20. Bovine IgG levels in product made using a serum containing cell culture may be high. An interim specification should be set for the IND submission.
- Centocor agreed to set an interim specification.

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