

Mid-Cycle Meeting Agenda/Summary

Application type and number: BLA 125683/0

Product name: Immune Globulin Subcutaneous (Human), 20% (b) (4)

Proposed Indication: Treatment of Primary Humoral Immunodeficiency (PI) in patients 2 years of age and older (1). This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies

Applicant: Grifols Therapeutics LLC

Meeting date & time: December 21, 2018; 9:00 a.m.

Committee Chair: Jennifer Reed

RPM: Candido Alicea

Attendees:

Discipline	Name	Attended meeting?
Regulatory Project Manager (RPM)	Candido Alicea	X
Chair	Jennifer Reed	X
Clinical Reviewer	Deborah Belsky	X
	Steve Winitsky	X
CMC Reviewer	Claire Wernly	X
	Hsiaoling Wang	X
	Tao Pan	X
	Maria Virata Theimer	
	Pei Zhang	
	Jing Lin	
Clinical Pharmacology Reviewer	Iftekhar Mahmood	
Toxicology Reviewer	Evi Struble	
OCBQ/DMPQ RPM	Sarah Lee	X
OCBQ/DMPQ Reviewer	Bradley Dworak	X
OCBQ/DMPQ/PRB Reviewer	Joseph Quander	
Statistical Reviewer of clinical data	Jiang Hu	X
Postmarketing Safety	Faith Barash	X
Epidemiological Reviewer		
OCBQ/APLB Reviewer	Stephanie Donahoe	X
	Alpita Popat	
	Oluchi Elekwachi	
OCBQ/BIMO Reviewer	Haecin Chun	
OCBQ/DBSQC or OVRP/LIB Reviewer	Varsha Garnepudi	
	Jing Lin	
Consult Reviewer(s)	Deborah Trout	
OCBQ/DMPQ/Lead Inspector		
CMC Inspector		
Labeling Reviewer	Stephanie Donahoe, Alpita Popat, Oluchi Elekwachi	X

Discipline	Name	Attended meeting?
Other Attendee(s)	Kim Benton	X
	Tejashri Purohit-Sheth	X
	Ilan Irony	X
	Michael Kennedy	X
	Dov Golding	X

Discussion Summary:

Most of the review team has completed their review or are near completion. No major issues have been reported although there are some IR (3) still pending responses. The Chair has already identified the need of a PMC for stability final report. Completion of all primary reviews projected to be before March 2019 (Late Cycle meeting 4/4/19)

Report and Discuss:

1. Reviewer Reports.

- a. **CMC – Product (PDB)** [*Jennifer L. Reed, Maria Luisa Virata-Theimer, Pei Zhang*] No issues have been identified that would preclude approval from the product perspective. PMC for stability final report will be required.

- Viral Safety – [Pei Zhang]
 - Viral Validation is performed in a scaled-down model at the following manufacturing steps:

(b) (4)

- Bioburden and Antimicrobial Effectiveness Test – [*Claire H. Wernly*] No substantive issues or major deficiencies have been found. Estimated date of completion, January 31, 2019.

b. **CMC- Product (DBSQC)**

- **Analytical method and validation** - [*Charlene Wang*]. Initial review of methods and validations is completed. The review of IR response (12/14/2018) is to be completed by Dec. 31.
- **Quality** – [*Tao Pan*] All the assigned assays have been reviewed, and IRs have been sent. Expect completion by Feb 28.
 - IR related to the validation of Polysorbate 80 assay;

- IR related to the validation of (b) (4) assay;
 - IR related to the validation of Caprylate assay;
 - IR related to the validation of Glycine (b) (4) assay
- **Lot release Protocol template** - [Varsha Garnepudi] A lot release protocol template has been requested through an IR. The Laboratory Quality Product Testing Plan (TP) has been initiated. Initial review should be complete by January 20, 2019.
- c. **CMC-DMPQ** – [Brad Dworak] Container Closure Sec. 3.2.S.6 is not completely reviewed at this time. Process validation for 18-22% protein concentration does not match the labelling of 20% protein. The DMPQ inspection waiver will depend on the outcome of Team Bio inspection. Review to be completed by June 9, 2019.
 - d. **Bioresearch Monitoring (BIMO)** - [Haecin Chun] Inspection of (b) (4) facility complete. Inspections of North Carolina, (b) (4) facilities are still pending. Primary review will be completed after all Establishment Inspection reports are received and reviewed.
 - e. **Clinical** - [Deborah S. Belsky] All sections reviewed. Preliminary written draft ready for review 12/20/2018.
 - i. Need to discuss with the Clinical Pharmacology Reviewer the adequacy of the pediatric PK data in satisfying the requirement in the Agreed iPSP.
 - ii. Of note, the BLA contains data for only a single subject in the age range of 2-5 years.
 - iii. If the pediatric data are not sufficient to label the product the applicant is conducting an ongoing study (GTI1503) that includes a pediatric cohort, and a PMR for completion of study GTI1503 can be issued.
 - f. Pharmacology/Toxicology [Evie Struble] **Information regarding review will be presented by reviewer.**
 - g. Clinical Pharmacology - [Iftekhar Mahmood] Review is ongoing, to be completed by March 2019.
 - h. BioStatistics [Jiang Hu] **Information regarding review will be presented by reviewer.**
 - i. OBE-Epidemiology - [Faith Barash] (Pharmacovigilance Plan) No substantive review issues have been identified. Reviewed safety data do not indicate a need for a REMS or a safety PMR.

- j. Advertising and Promotional Labeling [Stephanie Donahoe/ Alpita Popat]
Information regarding review will be presented by reviewer.

2. If the application will be discussed at an Advisory Committee (AC), review potential issues for presentation. **N/A**
3. Determine whether Postmarketing Requirements (PMRs), Postmarketing Commitments (PMCs), or a Risk Evaluation Mitigation Strategy (REMS) are needed.
 - A Title IX PMR requiring SWG review is not planned at his time.
 - PMC for stability final report will be required.
 - PMR for completion of study GTI1503 may need to be issued

4. National Drug Code (NDC) assignments to product/packaging.

The labeler code (NDC 13533) is assigned to Grifols USA, LLC. The NDCs for each packaging presentation are uniquely assigned.

5. Proper naming convention -
Suffixes were requested, sponsor has provided a list of suffixes.
6. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval and the establishment inspection report (EIR).

Inspection of (b) (4) facility is complete. Inspections of North Carolina, (b) (4) facilities are still pending.

Review

7. Major target and milestone dates from RMS/BLA. Discuss pending dates of targets and milestones (e.g. Late-Cycle meeting, Advisory Committee, labeling discussion).

Mid-Cycle Communication	1/9/2019
Late-Cycle Meeting	3/24/2019
Labeling Target	6/9/2019
PMC Study Target	6/9/2019
First Action Due	7/9/2019

8. Establish a labeling review plan and agree on future labeling meeting activities.

Labeling meeting will be scheduled following completion of the clinical review.

Confirm, as applicable

9. Components Information Table was obtained, and notification was sent to the Data Abstraction Team (DAT) if discrepancies were found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. If not complete, indicate date it will be completed. *[CMC Reviewer]*
10. New facility information is included in the application, requiring implementation of regulatory job aid (b) (4) [REDACTED] If not complete, indicate date it will be completed.

No new facilities.
11. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan. *[CMC Reviewer]*
12. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid (b) (4) [REDACTED] for additional information.

Will be sent by Dec 27.
13. PeRC presentation date is set, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision.

Please confirm that no PeRC meeting is needed.

Note: Remind the Review Committee that PeRC forms need to be submitted two weeks in advance of scheduled PeRC meeting.

14. Action Items:

- a. Confirm the Mid Cycle telecon date of January 9, 2019 at 3:00 p.m.
- b. Any substantive issues or need for consults?

15. For applications subject to the PDUFA Programs:

- a. The Late Cycle Meeting is planned for March 24, 2019.
- b. The Late Cycle Meeting Materials will be sent at least 10 days before the Late Cycle meeting.

The section below is only for those original applications that are subject to the PDUFA/BsUFA Programs

Mid-Cycle Communication Agenda/Summary

1. Any significant issues/major deficiencies identified by the Review Committee to date.

No significant issues have been identified at this time.

2. Information regarding major safety concerns. **Note:** there must be a pro-active statement included during the telecon regarding major safety concerns. The telecon summary must document the concerns discussed. If there are no major safety concerns at this time, the telecon summary must include a statement indicating there are none.

There are no major safety concerns identified at this time.

3. Preliminary Review Committee thinking regarding risk management.

At this moment there is no major deficiency.

4. Any information requests sent, and responses not received.

We are waiting for your response to our December 12, 18 & 19 information request. We want to let you to know that the delay would affect our review clock.

5. Any new information requests to be communicated. ?

6. Proposed date(s) for the Late-Cycle Meeting and the Late-Cycle Meeting Materials:

- a. To occur not less than 12 calendar days before the date of any AC meeting;
- b. To occur not later than 3 months (standard review) or 2 months (priority review) prior to the PDUFA goal date for applications not going to an AC meeting.

7. Updates regarding plans for the AC meeting, if appropriate.
TBD

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.