



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

To: To File (BLA STN **125587/0**)

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Applicant: Octapharma Pharmazeutika Produktionsges. M.b.H.

Product: Immune Globulin Intravenous, Human 10% (Panzyga®)

Subject: Final Review: original BLA, assigned CMC topics – Stability Section

RECOMMENDATION

This BLA submission is recommended for approval with the following conditions:

1. The proposed shelf life for drug product can't be granted, instead the following storage condition and shelf life is recommended: Drug product can be stored at 5 ± 3 °C for up to 24 months. Within its shelf life, this product can't be stored at ≤ 25 °C. This condition should be applied to product (b) (4) as well.
2. Post Market Commitment (PMC):
Octapharma commits to providing stability updates for the consistency lots manufactured in 2014 annually as a PMC annual report. The final stability report will be submitted as a PMC Final Study Report by November 4, 2016.

EXECUTIVE SUMMARY

Four materials were tested for their stabilities in the stability studies, i.e., (b) (4), and Final container product (Drug Product).

The proposed dating period of each material was evaluated based on the data from clinical lots, conformance lots, and consistency lots, and summarized as follows:

Materials	Proposed by Sponsor	Recommended by Agency
(b) (4)	(b) (4)	Acceptable
(b) (4)	(b) (4)	Acceptable
Drug Substance (b) (4)	(b) (4)	Acceptable

Drug Product (Final Container)	5 ± 3°C for up to 24 months; within its shelf life, the product was proposed to be stored at ≤ 25 °C for up to 6 months	To be stored at 5 ± 3 °C for up to 24 months; within its shelf life, this product can't be stored at ≤ 25 °C. This condition should be applied to product transportation as well.
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* For two clinical batches, (b) (4), antibodies against measles were below the limits of the specification at 1 month storage at +25 °C/(b) (4), and the data from both conformance and consistency lots are not available yet.

BACKGROUND INFORMATION

Panzyga is a 10% human normal IgG for intravenous administration (IGIV) in a liquid preparation, indicated for the treatment of primary humoral immunodeficiency and chronic immune thrombocytopenic purpura in adults.

During manufacturing of Panzyga, three storable intermediates, i.e., (b) (4), were produced. The final product (Drug Product) can be filled in configuration of 10 mL, 25 mL, 50 mL, 100 mL, 200 mL and 300 mL solution, supplied in (b) (4) glass vials with bromobutyl rubber stopper and aluminum flip off cap. Totally (b) (4) clinical bathes (manufactured from 2007 to 2011), (b) (4) conformance batches (manufacture in 2013), and (b) (4) consistency batches (manufactured in 2014) were placed under stability studies.

CMC REVIEW SUMMARY

This review encompasses the stability section from the original BLA submission.

- The submission was received on April 15, 2015.
- Updates of stability studies were received on July 31, 2015 (125587/0.11), and Oct 16, 2015 (125587/0.18), respectively.

1. STABILITY STUDY CONCEPT AND METHODS:

The purpose of this study is to provide guidance for assessing the proposed storage conditions and establishing the shelf life for the storable intermediates and final product, without sacrificing the specified product's potency, purity and quality.

Four types of materials are included in this stability study:

(b) (4)

(b) (4)

d) Drug Product (Final Container Product) – Panzyga is stored at 5 ± 3 °C, and the proposed shelf life is up to 24 months. Within the shelf life, the product may be subjected to 6 months of temperature excursion (25 °C). (b) (4) clinical lots, (b) (4) conformance lots, and (b) (4) consistency lots placed at the following conditions (table 4):

- i. 5 ± 3 °C (sampled at 0, 3, 6, 9, 12, 18, 24 months)
- ii. 25 °C/(b) (4) (sampled at 0, 3, 6, 9, (b) (4) months) - conformance and consistency lots only.
- iii. (b) (4)
- iv. (b) (4)
- v. Temperature excursion studies:
 - 1) For clinical lots, two temperature excursion studies were performed: study A: 25 °C/(b) (4) (0 to 1 month; (b) (4) months), 5 ± 3 °C (1-21 months) - sampled at 0, 1, 21, 24, 27 months; and study B: 5 ± 3 °C (0-18 months), 25 °C/(b) (4) ((b) (4) months) - sampled at 0, (b) (4) months.
 - 2) For conformance lots, one temperature excursion study was performed: 25 °C/(b) (4) (0 to 1 month; (b) (4) months), 5 ± 3 °C (1-(b) (4) months) - sampled at 0, 1, (b) (4) months.
 - 3) For consistency lots, one temperature excursion study was performed: 25 °C/(b) (4) (0 to 3 month; (b) (4) months), 5 ± 3 °C (1-(b) (4) months) - sampled at 0, 1, (b) (4) months.

The following test parameters are included (also see Appendix 1 in attachment):

- Clarity: the liquid preparation is clear or not more opalescent than the reference (b) (4)
- pH (4.5-5.0) (meets (b) (4))
- Protein composition: (b) (4) Immunoglobulin G
- (b) (4)
- (b) (4) Monomers and Dimers $\geq 90\%$; Fragments $\leq 3\%$.
- (b) (4)
- Diphtheria Ab (b) (4)
- Measles Ab (b) (4) NIH176 (During this review, sponsor agreed to change the measles antibodies' specifications from (b) (4) NIH 176 – also see specification review section; Malgorzata Norton).
- Polio Ab (b) (4) (Polio (b) (4)) NIH 176.
- (b) (4)
- IgG content: (b) (4)

2. RESULTS

(b) (4)

d) Final product:

For clinical and conformance lots, the stability studies were complete (table 4), and for consistency lots, the study is on-going with 6 months data being submitted. The overall stability tendency was assessed through statistical regression analysis:

- 1) Statistical approach: Analysis of Covariance (ANCOVA) was used to determine if the data from individual batches could be pooled across lots per ICH Q1A (R2) guidance. Briefly, (b) (4), (b) (4), will be selected based on the quality of intercepts and slopes tested at a significance level of (b) (4). For the models with (b) (4), the expiry date will be calculated based on the (b) (4) data; for the model with (b) (4), the expiry date will be calculated based on the worst lot scenario. The expiry date will be predicted as the maximum storage period within which the 95% confidence interval (CI) for the lot remains within the specification range. If the real time stability study in the proposed storage conditions supported the proposed shelf life, the data from other storage conditions will not be plotted unless it is needed for comparison purpose.
- 2) For storage condition at 5 ± 3 °C, all the results were met with specifications.
- i. For clinical lots, common slopes were applied to the parameters of pH, total protein, (b) (4), measles ab, polio ab, and different slopes were applied to monomers and dimers, and diphtheria antibody. For monomers and dimers and diphtheria antibody, lot (b) (4) and lot (b) (4) were identified as the

worst case scenario, respectively. No limitations of these two parameters were noticed with 24 months (Figure 4).

- ii. For conformance lots, common slopes were applied to pH, polio ab, (b) (4), diphtheria antibody, and different slopes were applied to measles antibody, total protein, and monomers and dimers (Figure 4). For measles antibody, lot (b) (4) was identified as the worst case scenario, which predicted a shelf life of less than 18 months (Figure 4). However since the real data at both 18 and 24 months were provided and found to be within specification, indicating the trending analysis did not reflect the real situation. Further analysis indicated that all lots, except (b) (4), have a common slope (Figure 5, upper panel) – the data at both 9 and 18 months were outside the clusters of data from other groups. When Lot (b) (4) and other lots (pooled) were plotted separately, the predicated shelf life is beyond 24 months (Figure 5, lower panel). For total protein and monomers and dimers, lot (b) (4) and lot (b) (4) were identified as the worst case scenario, respectively. No limitations for these two parameters were noticed with 24 months (Figure 4).
- iii. For consistency lots, up to 6 months of data were provided and were met with specifications. Since the potential limiting factors are identified as Fragments and Measles antibodies through different studies (see deviations below), these two parameters were analyzed along with the corresponding data from conformance lots (6 months). At both testing conditions (4 °C and 25 °C), all lots from consistency and conformance lots were found to have the common slopes (Figure 6 and Figure 7-fragments level at 4 °C storage condition remains below 1% for all batches and the data was not plotted), indicating that the stability data for both parameters between consistency lots and conformance lots are comparable. These may suggested that the consistency lots may remain stable within 24 months as indicated by conformance lots. The stability study is on-going and update of the stability will be requested as a PMC.

3) For storage conditions at 25 °C, (b) (4) the following deviations were noticed.

(b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

3. CONCLUSIONS

The proposed shelf life for (b) (4) was supported by real-time stability studies performed at the proposed storage conditions. The data for Final Product (Drug Product) supported a shelf life of 24 months but did not support the proposed storage at 25 °C within its shelf life due to the out of specifications events occurred for measles antibodies within 1 month at 25 °C. The temperature excursion studies for both conformance lots and consistency lots are still on-going, and the data will not become available during the BLA review period. The proposed storage condition at 25 °C within its shelf life can be re-evaluated upon request by the sponsor when the data become available.

The only limiting factor identified in determination of the shelf life is measles antibody. Although the real-time stability study for both conformance and consistency lots are considered to be complete for this BLA, the protocol showed that the studies will continue until (b) (4) months. In the long term, it is possible that sponsor will request for the shelf life extension, and the measles antibody may become the limiting factor of the shelf life at certain time points.

(b) (4)

(b) (4)

Table 4. Final Products

Types	Batches	Starting date	Tm (°C)	Months	Status
Clinical	(b) (4)	7 Jan 2010	5±3 °C Or 25 ^{(b) (4)} °C	(b) (4) months	Completed
		7 Jan 2010		months	Completed
		7 Jan 2010		months	Completed
		7 Jan 2010		months	Completed
		27 Jan 2010		months	Completed
		27 Jan 2010		months	Completed
		27 Jan 2010		months	Completed
		27 Jan 2010		months	Completed
		3 Feb 2010		months	Completed
		3 Feb 2010		months	Completed
		3 Feb 2010		months	Completed
		3 Feb 2010		months	Completed
		3 Feb 2010		months	Completed
Conformance	(b) (4)	18 Jul 2013	5±3 °C Or 25 ^{(b) (4)} °C	months	ongoing
		18 Jul 2013		months	ongoing
		24 Jul 2013		months	ongoing
		24 Jul 2013		months	ongoing
		26 Jul 2013		months	ongoing
		26 Jul 2013		months	ongoing
		14 Aug 2013		months	ongoing
		09 Aug 2013		months	ongoing
		14 Aug 2013		months	ongoing
		14 Aug 2013		months	ongoing
		09 Aug 2013		months	ongoing
		14 Aug 2013		months	ongoing
		14 Aug 2013		months	ongoing
		20 Aug 2013		months	ongoing
		20 Aug 2013		months	ongoing
		20 Aug 2013		months	ongoing
		20 Aug 2013		months	ongoing
		03 Sep 2013		months	ongoing

Consistency	(b) (4)	23 Jan 2015	5±3 °C	6 months	ongoing
		23 Jan 2015	Or	6 months	ongoing
		23 Jan 2015	25 ^{(b) (4)} °C	6 months	ongoing
		23 Jan 2015		6 months	ongoing
		23 Jan 2015		6 months	ongoing
		04 Feb 2015		6 months	ongoing
		23 Jan 2015		6 months	ongoing
		23 Jan 2015		6 months	ongoing
		23 Jan 2015		6 months	ongoing
		23 Jan 2015		6 months	ongoing
		04 Feb 2015		6 months	ongoing
		04 Feb 2015		6 months	ongoing
		23 Jan 2015		6 months	ongoing
		23 Jan 2015		6 months	ongoing
		02 Mar 2015		6 months	ongoing
		02 Mar 2015		6 months	ongoing
		02 Mar 2015		6 months	ongoing
		02 Mar 2015		6 months	ongoing

(b) (4)

