



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

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Subject: Original BLA
Product: Intravenous Immune Globulin, 10% (Human; IgG Next Generation, BT595)
Submission Date: June 30, 2023
Sponsor: Biotest

Summary and Recommendation: Approval with the following PMCs:

- Biotest commits to providing the complete leachables data supporting the BT595 PPQ drug product batches manufactured from US plasma in BE-186-95 as a Postmarketing Commitment Submission – Final Study Report by December 31, 2024
- Biotest commits to providing the final CAPA report for 200195300 as a Postmarketing Commitment Submission – Final Study Report by November 30, 2024.
- Biotest commits to providing the complete stability data supporting BT595 PPQ drug product batches manufactured from US plasma in study BE-Q-301j/95/03 as a Postmarketing Commitment Submission – Final Study Report by November 30, 2024.

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Introduction:

- IgG Next Generation (BT595) is a 10% intravenous immunoglobulin product intended for the treatment of primary humoral immunodeficiency (PI).
- At the firm's facility in Dreieich, Germany, BT595 is manufactured from large pools of human plasma via a (b) (4) cold ethanol fractionation process, with further purification by caprylate precipitation and chromatography steps.
- A process (b) (4) designated Process (b) (4) was implemented after the clinical study was performed. Process (b) (4) comparability was evaluated in a PPQ campaign of (b) (4) batches manufactured on dedicated US equipment from US source plasma.
- Data and information regarding drug product specifications, manufacturing impurities including extractables and leachables, and stability of Process (b) (4) PPQ batches, are reviewed in the current memo. In addition, the firm's final deviation report regarding (b) (4) repeatedly detected in its (b) (4) is evaluated.

Final Product Characteristics and Specifications

BT595 IgG Next Generation is a polyvalent human immunoglobulin solution for intravenous administration. The IgG is provided as a 100 mg/ml solution which is clear to slightly opalescent, colorless to pale yellow, and is provided in 50, 100, and 200 ml vials. The final product contains Glycine (b) (4) micromoles/ml) and Polysorbate 80 (b) (4) micrograms/ml) as excipients/stabilizers. The final container is clear, colorless type (b) (4) vials, closed with Type (b) (4) bromobutyl rubber stoppers and flip-off aluminum caps. Final agreed Drug Product specifications are listed in Table 1, below.

Table 1: Drug product specifications of IgG Next Generation

Determination	Requirement	Method	SOP
(b) (4)	Complies	(b) (4)	SOP-Q-00100
Antibody to hepatitis B surface antigen	(b) (4)		SOP-Q-00591
Polio virus neutralization potency			(b) (4)
(b) (4)	(b) (4) CBER Ref Std (b) (4) (b) (4)		
Measles virus neutralization	(b) (4) CBER Ref Std (b) (4) (b) (4)		
Diphtheria toxin neutralization potency	(b) (4)		

Coloration	Equal or less colored than reference solution (b) (4)	(b) (4)	SOP-Q-00311	
Clarity and opalescence	Equal or less opalescent than reference solution (b) (4)	(b) (4)	SOP-Q-00515	
Visible particles	Clear and practically free from particles	Visual inspection	SOP-Q-00262	
Extractable volume	NLT nominal	(b) (4)	SOP-Q-00197	
pH	4.4-5.2		SOP-Q-00050	
Osmolality	280-380 mosmol/kg		SOP-Q-00336	
Total Protein	90-110 g/l		SOP-Q-00593	
(b) (4)			SOP-Q-00100	
			SOP-Q-00100	
			SOP-Q-00102	
			SOP-Q-00455	
			SOP-Q-00455	
			SOP-Q-00455	
			SOP-Q-00455	
			SOP-Q-00455	
			SOP-Q-00455	
			SOP-Q-00360	
Composition of immunoglobulins -			SOP-Q-00257	
			SOP-Q-00110	
			SOP-Q-00110	
IgG	(b) (4)	(b) (4)	SOP-Q-00110	
IgM	(b) (4)		SOP-Q-00110	
IgA	NMT 300 ug/ml		SOP-Q-00259	
(b) (4)			SOP-Q-00441	
			SOP-Q00417	
			SOP-Q-00419	
			SOP-Q-00440	
Sterility	Sterile	(b) (4)	SOP-Q-00168	
Bacterial endotoxins	(b) (4)			
Polysorbate 80	2-20 ug/ml			
Glycine	270-330 mmol/l			

Stability: Final Product

Study BE-T:Q-301h-95 evaluated stability of BT595 PPQ “Process (b) (4)” batches manufactured from US plasma to support the clinical trial, and commercial batches manufactured from EU plasma. For samples of 100ml, 50ml, and 200ml fill sizes, the firm provided (b) (4) months of stability at 2-8°C; (b) (4) months of stability information at 25°C; plus accelerated stability information (b) (4) 24 months, and (b) (4) 6 months). The study is completed, with no problematic data or trends identified. The firm proposed a shelf life of 30 months at 5°C with a one-time storage of up to 6 months at room temperature (NMT 25°C).

Subsequently the firm initiated study BE-T:Q-301j-95, which evaluated samples of (b) (4) batches, filled at 50ml, 100ml, and 200ml sizes, from the “Process (b) (4)” PPQ campaign. The stability profiles of Process (b) (4) lots appear very similar to Process (b) (4) batches (Attachments 1-3). The study is ongoing; data submitted cover 24 months of shelf life with no problematic trends. The firm has agreed to submitting the final study report as a postmarketing commitment. No specific concerns have been identified.

Overall, the data support the firm’s suggested shelf life of 30 months at 5°C with a one-time storage of up to 6 months at room temperature (NMT 25°C).

Note: The firm submitted additional stability data to support (b) (4) (b) (4) Due to insufficient validation data, the proposals to manufacture BT595 utilizing (b) (4) have been removed from the current submission. For this reason, the stability data supporting (b) (4) and (b) (4) from the firm.

Manufacturing Process Impurities Description

The firm provided a list of the major process- related impurities and the manufacturing step(s) which (b) (4) as detailed below.

(b) (4)

7 pages have been determined to be not releasable: (b)(4)

(b) (4)

References

Jenke D and Carlson T. 2014. A compilation of safety impact information for extractables associated with materials used in pharmaceutical packaging, delivery, administration, and manufacturing systems. PDA J Pharm Sci and Tech 68: 407-455.

US DHHS/ FDA/ CDER/CBER. 2021. QC3 (R8) Impurities: Guidance for Residual Solvents, Guidance for Industry.