



Memorandum

To: BLA STN 125810/0 File

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Through: Jennifer L. Reed, Ph.D., Branch Chief, PDB2/DPD/OPPT/OTP/CBER
Dorothy Scott, M.D., Division Director, DPD/OPPT/OTP/CBER

CC: Mona Badawy, RPM, DRMRR/ORMRR/OTP/CBER

Applicant: Biotest AG, Dreieich, Germany

Product: Immune Globulin Intravenous, Human – dira, 10%
Proposed trade name: YIMMUGO®

Subject: CMC Review: Original BLA – Drug Substance and Drug Product Specifications, selected Analytical Procedures and their Validation Studies assigned to the Product Office, Control of Materials (Serological and Nucleic Acid Testing of plasma for bloodborne pathogens)

Recommendation

Approval, with the following Post-marketing Commitment as agreed upon by the sponsor on 20-MAY-2024:

Biotest commits to implementing the (b) (4) test for Drug Product lot release and setting the specification based on Drug Product testing results. The (b) (4) method SOP and the validation study report for testing DP will be submitted as a Prior Approval Supplement (PAS) no later than September 30, 2024. In the interim, Biotest commits to testing for (b) (4) in the (b) (4) with a specified limit of (b) (4) until the PAS is approved.

Final Report Submission: September 30, 2024

Executive Summary

This Discipline Review memorandum covers assigned CMC sections of the Original Biologics License Application (BLA) submission from Biotest AG for their Immune Globulin Intravenous, Human – dira, 10% (IGIV) product, YIMMUGO®, which is proposed for the treatment of primary humoral immunodeficiency (PID) in patients 2 years of age and older, received by FDA CBER on 30-JUN-2023. The CMC sections I reviewed were: Control of Materials [serological and Nucleic Acid Test (NAT) testing of plasma for bloodborne pathogens], (b) (4) Drug Product (DP) Specifications, Analytical Procedures and their Validation Studies that are usually assigned for Product Office review, which included: Antibody to hepatitis B surface antigen (Anti-HBs), (b) (4) (b) (4) Identity, Appearance, (b) (4) Polio virus neutralization potency, Measles virus neutralization potency, and (b) (4). In general, the most of the abovementioned specifications, analytical procedures and validation studies, and other information

CMC Product Final Review - BLA STN 125810/0 ML Virata

provided by the sponsor appeared to be adequate and acceptable. However, several product-related CMC issues required one or more Information Requests (IR) to the sponsor before they were resolved: (b) (4) in the Process Performance Qualification (PPQ) lots and a test method modification, addition of DP lot release specifications for the (b) (4) and (b) (4) test, correction of their Post-Packaging Identity Test protocol, adjustment of their Measles virus neutralization potency specification, revision of their Composition of Immunoglobulins (IgG/IgA/IgM) and Antibody to hepatitis B surface antigen (Anti-HBs) specifications. The sponsor agreed to a PMC to implement (b) (4) testing for DP lot release and to submit the method SOP and final validation study report as a PAS by September 30, 2024 (see PMC #2e).

Background Summary

FDA CBER received on 30-JUN-2023 this Original BLA from Biotest AG (dated 30-JUN-2023) for their Immune Globulin Intravenous (Human) – 10% product, YIMMUGO® (also referred to as IgG Next Generation, BT595, by the sponsor) which is proposed for the treatment of primary immunodeficiency (PID) in patients 2 years of age and older. This IGIV 10% product is manufactured only from U.S. Source Plasma using a (b) (4) cold ethanol fractionation process with caprylic acid precipitation, pH^{(b) (4)} treatment, anion- and cation-exchange chromatography and nanofiltration. YIMMUGO is formulated in Water for Injection containing 0.27-0.33 mmol/mL glycine, 2-20 µg/mL polysorbate 80, with a pH of (b) (4) and filled into 50 mL (5 g), 100 mL (10 g) and 200 mL (20 g) type (b) (4) glass vials.

Jennifer L. Reed, Ph.D. of PDB2/DPD/OPPT/OTP is the Review Committee chair of this BLA submission. My CMC review focused on the following sections: Control of Materials (particularly serological and NAT testing of plasma for bloodborne pathogens), (b) (4) DP Specifications, selected Analytical Procedures and their Validation Studies usually assigned to the Product Office: Anti-HBs, (b) (4) (b) (4) Identity, Appearance, (b) (4) Polio virus neutralization potency, Measles virus neutralization potency, (b) (4) and Extractable Volume. The other Analytical Procedures and their Validation Studies such as: pH, Diphtheria toxin neutralization potency, Osmolality, Total Protein, Protein Composition, Protein Concentration, (b) (4) Bacterial Endotoxins, Sterility, Glycine, Polysorbate 80, IgG/IgA/IgM were reviewed by DBSQC/OCBQ reviewers (see their Discipline Review memos). Leonid Parunov, Ph.D. of HB2/DH/OPPT/OTP was the Consult Reviewer for the (b) (4) (b) (4) assays (see his review comments below in Section B, no. 2k). George Kastanis of QAB/DBSQC/OCBQ reviewed the lot release protocol template (see his review memo).

CMC Review Summary

For the majority of Biotest's proposed (b) (4) DP specifications, the acceptance criteria appeared to be similar or not significantly different from those set for other US-licensed IGIV 10% products (see Section B, no. 1 below for (b) (4) DP tables with testing data). Most of the justifications provided by the sponsor appeared to be acceptable. Batch analysis data met the set acceptance criteria. For the Analytical Methods and Validation Studies reviewed by the Product Office, most of their method SOPs were based on (b) (4) test methods (b) (4). Their validation studies were performed according to (b) (4) guidelines on Analytical Method Validation, and the validation study data appeared adequate and acceptable. With regards to Control of Materials, particularly the serological and NAT testing of plasma for bloodborne pathogens, the method SOPs and validation data appeared adequate and acceptable. However, there were a few product-related CMC issues that needed further investigation, clarification, and revision (see Section A below).

A. Product-related CMC Issues:

1. Investigation of the Higher (b) (4) in PPQ Process (b) (4) lots compared to the clinical trial Process (b) (4) lots, the possible risk of hemolysis, (b) (4) test method modification

Process (b) (4) IGIV lots were used in Biotest's clinical trial studies for PID and immune thrombocytopenic purpura (ITP). However, for the full-scale manufacturing process, the PPQ conformance lots were manufactured slightly differently using Process (b) (4) which included several changes to the in-process manufacturing parameters and the use of (b) (4) (b) (4) testing by Biotest showed that the (b) (4) IGIV lots had (b) (4) (b) (4) compared to the (b) (4) IGIV lots (b) (4) all still met the maximum allowable limit of (b) (4)

Dr. Yonggang Wang of PDB1/DPD/OPPT/OTP/CBER was requested by our DPD Director Dr. Dorothy Scott to perform direct hemagglutination testing of the (b) (4) and (b) (4) lots and he confirmed Biotest's results. In addition, Dr. Wang also tested the lots for hemolytic activity, using an in-house complement-dependent hemolysis assay, and showed that even though the (b) (4) IGIV lots' (b) (4) were lower than those of the (b) (4) IGIV lots, their hemolytic activity levels were similar to those of some older clinically hemolytic lots of another 10% IGIV product, Privigen® (CSL Behring AG), which also has a (b) (4) treatment step (see Appendix below for Dr. Wang's data slides). Published studies have reported higher hemagglutinin titers and hemolytic adverse events associated with immunoglobulin products purified via caprylate/chromatography steps compared to products made without caprylate (Romberg *et al*, 2015)

Because there were concerns over the possible risk of hemolysis with these (b) (4) lots, more (b) (4) (b) (4) test data was requested from Biotest in an Information Request (IR) sent on 10-AUG-2023. Biotest provided a data table of US and EU batches of BT595 manufactured after the comparability campaign using the (b) (4) manufacturing process since (b) (4) (Amendment 5, dated/received 15-AUG-2023). The (b) (4) ranged from (b) (4) to (b) (4) while the (b) (4) ranged from (b) (4) to (b) (4). All lot results met the set (b) (4) acceptance criteria of (b) (4). This (b) (4) limit is commonly used by the majority of the IGIV manufacturers.

During the Late-Cycle Meeting (LCM) on 14-MAR-2024, Biotest pointed out that their (b) (4) (b) (4) detection method (SOP-Q-00259), which is based on the (b) (4) (b) (4) had also undergone some changes. After the LCM, the following information were provided by Biotest: the change history of their method SOP, an overview of the (b) (4) of clinical trial 991 and PPQ batches and positive standards (Responses 3a and 3b, Amendment 71, dated 28-MAR-2024, received 8-APR-2024), the investigation and assessment of the method change (Amendment 78, dated/received 25-APR-2024).

(b) (4) lots were tested using method SOP versions 1.1, 2.0 and 3.0, while (b) (4) PPQ lots were tested using method SOP version 6.0. Starting from method SOP version 4.0, Biotest changed the way they (b) (4) They implemented (b) (4)

If tested under the same conditions using the same type of (b) (4) the (b) (4) and (b) (4) lots could have had comparable (b) (4)

It should be noted that, as early as the pre-BLA meeting on 3-APR 2023, recommendations to reduce their (b) (4) titers were already conveyed to Biotest, namely, to screen their plasma and select only plasma lots with (b) (4) levels of (b) (4) and to incorporate an (b) (4) step into their manufacturing process. Biotest replied that they have developed an (b) (4) step in the (b) (4) process and that further development was ongoing. They had also evaluated possible strategies for plasma selection but determined that this is not feasible for them in the long term, due to the limited availability of very (b) (4) and that the screening effort can be very high,

depending on the degree of plasma selection and pooling strategy. In addition, they commented that plasma selection will not provide a sufficient amount of (b) (4). Biotest said that they will investigate the alternative of measuring (b) (4) in the manufacturing pool and consider how to use these results for better control of the final (b) (4) (b) (4) in the DP (Response 2, Amendment 2, dated/received 8-AUG-2023).

2. Addition of the (b) (4) for DP lot release

Majority of the US-licensed IGIV products have a (b) (4) specification for DP lot release. There was (b) (4) specification listed for (b) (4) DP lot release in the initial BLA submission, therefore, the following IR was sent to the sponsor on 28-JUL-2023:

eCTD 3.2.S.4.1 or 3.2.P.5.1 Specifications – The (b) (4) test and specification are missing from your list of lot release tests and specifications for (b) (4) (b) (4) Drug Product. Most of the FDA-approved Intravenous immunoglobulin products have a validated (b) (4) test and specification (and for some, an additional validated (b) (4) test and specification) in place to monitor for any (b) (4) impurities. Please consider adding these tests to your routine lot release testing of the IgG Next Generation (BT595) (b) (4) (b) (4) Drug Product.

In Biotest's response to the IR (Response 3, Amendment 3, dated 9-AUG-2023, received 10-AUG-2023), they mentioned that they have a validated (b) (4) assay (VAL-Q-00053_REP-01), but did not list it because they were considering discontinuing the (b) (4) test. They said that their (b) (4) step effectively removes the (b) (4) impurities to the point that they are undetectable, i.e., below their (b) (4) assay's limit of detection (LOD) of (b) (4). They intend to test at least (b) (4) commercial DP lots for (b) (4) activity to make sure this is indeed the case before they decide to discontinue (b) (4) testing. The Biotest (b) (4) specification is set at (b) (4) per the (b) (4) (refer to the Biotest slide presentation in Appendix 1 of the Application Orientation Meeting and Dataset Walkthrough document, Amendment 4, dated 7-AUG-2023, received 10-AUG-2023).

Since testing for (b) (4) and/or for (b) (4) at the DP lot release stage is currently the industry standard, the Product Office insisted that Biotest should keep their (b) (4) test in place for lot release testing. The following IR was sent to Biotest on 30-APR-2024:

Please amend your Drug Product release specifications to include (b) (4) (b) (4) as per the IGIV industry standard. Please justify the specifications with supporting data from Process (b) (4) conformance lots, as well as the statistical analysis.

In the sponsor's response to the IR (Amendment 81, dated 3-MAY-2024, received 6-MAY-2024) Biotest finally agreed to amend their DP lot release testing and specifications list by adding a (b) (4) as a mandatory test and setting the specification as (b) (4) (b) (4). The corresponding eCTD sections were also updated to reflect this change. This IR response and updates to the affected eCTD sections are acceptable.

Dr. Leonid Parunov of HB2/DH/OPPT/ OTP/CBER reviewed Biotest's method SOPs and validation data and found them to be acceptable (see his review comments below in Section B, no. 2k).

3. Addition of the (b) (4) specification for DP lot release

The (b) (4) treatment step is for the removal and/or inactivation of (b) (4) impurities. However, there was no (b) (4) specification listed for (b) (4) DP lot release in the initial BLA submission, therefore, the following IR was sent to the sponsor on 28-NOV-2023:

eCTD 3.2.S.4 Control of (b) (4) or 3.2.P.5 Control of Drug Product - (b) (4) (b) (4) test and specification are missing from your list of lot release tests and specifications for (b) (4) (b) (4) Drug Product (DP). Most of the FDA-approved immunoglobulin products, which have a (b) (4) manufacturing step, have a validated test and specification at either the (b) (4) DP lot release stage. Please consider adding this test to your routine lot release testing of the IgG Next Generation (BT595) (b) (4) (b) (4) Drug Product.

Biotest responded to this IR stating they do not consider having a (b) (4) specification at either the (b) (4) DP lot release stage to be necessary (Response 2, Amendment 34, dated 8-DEC-2023, received 12-DEC-2023). They have tested for (b) (4) in (b) (4) batches of (b) (4) treated (b) (4) from US Source Plasma manufactured with the (b) (4) process at commercial scale, using a validated (b) (4) determination test (VAL-Q-00055_REP-01), and confirmed that it is consistently removed (mean of (b) (4)). They plan to test at least (b) (4) commercial lots of YIMMUGO for (b) (4) in the (b) (4)-treated (b) (4) before they decide to discontinue the testing of every YIMMUGO (b) (4) lot.

This Product Reviewer checked again the (b) (4) specifications of other US-licensed immune globulins that have (b) (4) step in their manufacturing process and confirmed that tests for (b) (4) are indeed being done at the DP lot release stage. The following second IR was sent to the sponsor on 30-APR-2023:

Please amend your Drug Product release specifications to include (b) (4) and (b) (4) as per the IGIV industry standard. Please justify the specifications with supporting data from Process (b) (4) conformance lots, as well as the statistical analysis.

In their response to the IR (Amendment 81, dated 3-MAY-2024, received 6-MAY-2024), Biotest reiterated their previous response in Amendment 34. They also pointed out the additional results of PPQ batches in Table 3.2.S.3.2-1 that prove the removal of (b) (4) to levels below the limit of quantification (b) (4) of the test method. In addition, they referred again to the (b) (4) in (b) (4) in Table 3 of Attachment 2 (Amendment 26, dated 1-NOV-2023, received 3-NOV-2023). Biotest said they will include the (b) (4) test for the lot release of the (b) (4) with a limit of (b) (4). They consider testing for (b) (4) at this process step to be appropriate as this follows immediately after the (b) (4) steps in the manufacturing process and that no additional (b) (4) (b) (4) is applied afterwards.

Because their IR response was deemed to be unsatisfactory, a third IR was sent to Biotest on 6-MAY-2024 to further clarify FDA's request for them to test for (b) (4) as a (b) (4) DP lot release test:

We have received your rationale for excluding (b) (4) testing at the (b) (4) Drug Product release stage.

We understand your in-process (b) (4) determination method is validated for the (b) (4) (b) (4) and that your manufacturing steps have been designed to remove (b) (4) to very low levels.

We nevertheless request testing for (b) (4) at the (b) (4) Drug Product step to provide additional assurance of product quality in the event there is a manufacturing process discrepancy or error.

Measurement of (b) (4) in Immune Globulin products manufactured using this chemical is the current industry standard for US products. Please revise your specifications to include (b) (4) testing.

In their response to this third IR (Amendment 85, dated 8-MAY-2024, received 10-MAY-2024), Biotest finally agreed to implement (b) (4) testing as a DP lot release test. They proposed to set the DP specification at (b) (4) which corresponds to their results from testing the (b) (4). They plan to submit the method SOP and validation for DP as a Prior Approval Supplement (PAS) no later than September 30, 2024. In the meantime, they will test for (b) (4) at the (b) (4) stage with the abovementioned limit until the PAS is approved. Product Office reviewers disagreed with Biotest's proposal of setting the DP limit at (b) (4) based on the results of the (b) (4) since they will be allowing a maximum concentration that is still quite high (for comparison, Privigen's DP limit is (b) (4)). The Product Office requested Biotest to set their specification based on their DP testing results – see proposed PMC below which was included in the PMCs Communication sent on 14-MAY-2024.

Biotest commits to implementing the (b) (4) for Drug Product lot release and setting the specification based on Drug Product testing results. The (b) (4) method SOP and the validation study report for testing DP will be submitted as a Prior Approval Supplement (PAS) no later than September 30, 2024. In the interim, Biotest commits to testing for (b) (4) in the (b) (4) with a specified limit of (b) (4) until the PAS is approved.

Biotest responded on 17-MAY-2024 (Amendment 90, received 17-MAY-2024) and then re-sent their IR response with corrections on 20-MAY-2024 (Amendment 91, received 20-MAY-2024). In both IR responses, they agreed to do the PMC.

4. Correction of the Post-Packaging Identity Test

It was not clearly stated in the initial BLA submission whether Biotest was testing the finished product for Identity at the post-labeling/post-packaging stage. The following IR was sent to the sponsor on 28-NOV-2023:

eCTD 3.2.P.5 Control of Drug Product – According to 21 CFR 610.14, Identity Testing is required for identifying the Drug Product correctly after it has been filled, labeled and packaged. Your Identity Test method SOP-Q-00100 (b) (4) and your method validation report VAL-Q-00146_REP-01 V1.0 do not state specifically whether you are performing the Identity Test at the post-labeling/post-packaging stage. Please update your method SOP with additional instructions to cover the Identity Testing of the Drug Product at the post-labeling/post-packaging stage and re-validate the test performance at this particular stage. After making the requested revisions and revalidation, please submit the updated method SOP, updated method validation report and updated list of specifications (if Identity Testing wording needs to be revised).

In Biotest's response to the IR (Amendment 34, dated 8-DEC-2023, received 12-DEC-2023), they described their Identity Testing as follows: They perform the Identity Testing for YIMMUGO by (b) (4) with adequate controls ensuring the identity. They have also evaluated the risk for this approach and concluded that after the (b) (4) testing, there is adequate control for the lot throughout the (b) (4) (b) (4) thus ensuring the identity of the product.

The Product Office disagreed with the sponsor's approach, particularly with the timing of their (b) (4) testing, which is done (b) (4) (b) (4) has completed) and that after (b) (4) they will only confirm the identity by verifying the (b) (4).

(b) (4) Performing the Identity Testing in this manner does not meet the 21 CFR 610.14 requirements. Comments on their approach were conveyed to Biotest in this second IR sent on 14-FEB-2024:

Your Post-Packaging Identity Test protocol consisting of verification of the (b) (4) (b) (4) does not comply with current regulations, outlined in General Biological Products Standards, concerning product identity [21 CFR 610.14]. Please submit your proposal for a post-packaging test that established identity through the physical or chemical characteristics of the product after all labeling and packaging have been completed.

In Biotest's response to this second IR (Amendment 60, dated 27-FEB-2024, received 28-FEB-2024), they stated that they will implement the (b) (4) (SOP-Q-00100) as a Post-Packaging Identity (PPID) Test before the production of the first US commercial YIMMUGO lot. Their proposal of using (b) (4) to identify the IGIV 10% product by its (b) (4) (b) (4) after the packaging process is acceptable as a PPID Test and meets the 21 CFR 610.14 requirements.

5. Adjustment of Measles Virus Neutralization Potency specification for DP lot release

Biotest had proposed initially a Measles Virus Neutralization Potency specification of (b) (4) CBER Reference Standard (b) (4) for DP lot release. Typically, other US-licensed IGIV products have anti-measles limits set at (b) (4) x CBER Reference Standard". It was not clear how Biotest decided on this value, since their PPQ lots' DP results ranged from (b) (4) CBER Reference Standard". The following IR was sent to the sponsor on 8-MAY-2024:

Please round your Measles Virus Neutralization Potency specification up to (b) (4) CBER Reference Standard (b) (4) or alternatively, send your calculations justifying the current limit.

In their IR response (Amendment 89, dated/received 10-MAY-2024), Biotest agreed to round up their anti-measles specification to (b) (4) CBER Reference Standard (b) (4) eCTD sections 3.2.P.5.1 and 3.2.P.5.6.4 were updated accordingly with the new value. Biotest stated that as the document STD-Q-00181 "Specification of the IgG Next Generation (BT595) drug product" is valid for both US and non-US manufacturing, they will change it after BLA approval in order to be compliant with the approved (b) (4) Their IR response is acceptable.

6. Revision of Composition of Immunoglobulins Specification

In the initial BLA, Biotest proposed a Composition of Immunoglobulins specification of (b) (4) 96% IgG, (b) (4) IgA, and (b) (4) IgM". For other US-licensed IGIV products, their IgA and IgM specifications are usually expressed in g/L or mg/mL. After comments were made on the draft package insert about the unitage of the IgA content stated there vs. the DP lot release specification, an IR was sent to Biotest on 22-MAY-2024 requesting them to make the following changes to their specifications:

Composition of Immunoglobulins Specification:

- a. For clarity and consistency, please state IgG, IgA, and IgM content in milligrams / mL rather than percent.*
- b. IgA Specification: Please revise specification to NMT 0.3 milligrams per mL.*

In their IR response (Amendment 96, dated/received 24-MAY-2024), Biotest proposed to revise their Composition of Immunoglobulins specification to: (b) (4) IgG, (b) (4) IgA and (b) (4) IgM". They agreed to revise their IgA specification to (b) (4) as recommended in the IR, which is acceptable. However, in converting their IgG and IgM limits from percent to

mg/mL, they decided to (b) (4) respectively. The Product Reviewers disagreed with their approach and found their IgG minimum to be set too low (all their IgG DP results were (b) (4) (b) (4) and their IgM maximum to be set too high (all their IgM DP results are (b) (4) (b) (4) IgG and (b) (4) (b) (4) IgM” as the more acceptable IgG and IgM specifications for DP lot release based on their PPQ DP testing results.

Composition of Immunoglobulins Specification:

- a. Please revise IgG specification to (b) (4)
- b. Please revise IgM specification to (b) (4)

In Biotest’s response to this second IR (Amendment 98, dated 27-MAY-2024, received 28-MAY-2024), they agreed to set their IgG and IgM specifications to the limits recommended by the Product Reviewers. The specifications in their draft Lot Release Protocol were also revised accordingly.

7. Revision of Antibody to Hepatitis B Surface Antigen Specification

In the initial BLA, Biotest proposed an Antibody to Hepatitis B Surface Antigen (Anti-HBs) specification of (b) (4) based on their PPQ DP lot test results. Other US-licensed IGIV products, however, express their Anti-HBs specifications in IU/g IgG or IU/mL, and their Anti-HBs minimum limits typically set at (b) (4) IgG.” The following IR was sent to Biotest on 29-MAY-2024:

Antibody to hepatitis B surface antigen specification:

Per the US lot release specification for Anti-HBs, please revise your Anti-HBs specification to (b) (4) IgG.

In Biotest’s response to this IR (Amendment 102, dated 31-MAY-2024, received 31-MAY-2024), they agreed to set their Anti-HBs specification to the limit recommended by the Product Reviewers. The specification in their Lot Release Protocol template was also revised accordingly.

B. Review of Assigned CMC Sections

Manufacture, aseptic filling, labeling, packaging, in-process and most of the lot release testing of IGIV 10% are performed at the Biotest AG manufacturing facility in Dreieich, Germany. Only the lot release tests for Diphtheria Toxin Neutralization Potency, Measles Virus Neutralization Potency, Polio Virus Neutralization Potency are performed externally by (b) (4) in different locations (b) (4) (primary testing laboratories), (b) (4) (alternative testing laboratory)] and by (b) (4) in the (b) (4) (alternative testing laboratory).

1. (b) (4) Drug Product Specifications, Justifications of Specifications

The (b) (4) Drug Product (DP) specifications proposed for YIMMUGO were based on prior knowledge of other IGIV products and were verified by testing (b) (4) clinical lots (manufactured between (b) (4) to (b) (4)), (b) (4) PPQ (b) (4) lots and (b) (4) PPQ DP lots (manufactured between (b) (4) to (b) (4)). In order to be consistent with other US-licensed IGIV products, the Product Office requested Biotest to adjust or revise a few of their specifications, namely: Measles Virus Neutralization Potency, Composition of Immunoglobulins – IgG/IgA/IgM, and Antibody to hepatitis B surface antigen. For the same reason, (b) (4) tests and specifications were also requested to be added to the DP lot release testing: (b) (4) (b) (4)

Table 1: Proposed Specifications for IGIV 10% (b) (4)
CMC Product Final Review - BLA STN 125810/0 ML Virata

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

(b) (4)

Table 2: Proposed Specifications for IGIV 10% Drug Product

Test Parameter	Analytical Procedure Reference Method SOP No.	Final Acceptance Criteria	Justification for Specification	Clinical Lot Acceptance Criteria <i>Results</i> (N= (b) (4))	PPQ/Validation Lots Acceptance Criteria <i>Results</i> (N = (b) (4))
Identity (b) (4) (b) (4) <i>To be performed post- packaging per 21 CFR 610.14</i>	(b) (4) (b) (4)	Complies	Qualitative indication that the drug product consists of human immunoglobulin.	Complies <i>All results complied.</i>	Complies <i>All results complied.</i>
Antibody to Hepatitis B Surface Antigen (Anti-HBs)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Polio Virus (b) (4) Neutralization Potency (b) (4)	(b) (4)	(b) (4) CBER Ref Std (b) (4)	Per 21 CFR 640.104, each final product lot shall contain at least the minimum levels of antibodies for at least one type of poliomyelitis (b) (4)	(b) (4) CBER Ref Std (b) (4) (b) (4) CBER Ref Std	(b) (4) CBER Ref Std (b) (4) (b) (4) (b) (4) CBER Ref Std (b) (4)

Polio Virus (b) (4) Neutralization Potency (b) (4)	(b) (4)	(b) (4) CBER Ref Std (b) (4)	Release limit is based on the IGIV potency requirement of FDA.	-----	-----
Measles Virus Neutralization Potency (b) (4)	(b) (4)	(b) (4) CBER Ref Std (b) (4)	Per 21 CFR 640.104, each final product lot shall contain at least the minimum level of antibodies for measles. Release limit is based on the IGIV potency requirement of FDA.	(b) (4) CBER Ref Std (b) (4) (b) (4) CBER Ref Std	(b) (4) CBER Ref Std (b) (4) (b) (4) CBER Ref Std (b) (4)
Measles Virus Neutralization potency (b) (4)	(b) (4)	(b) (4) CBER Ref Std (b) (4)		-----	-----
Diphtheria Toxin Neutralization Potency (b) (4)	(b) (4) (b) (4)	(b) (4)	Per 21 CFR 640.104, each final product lot shall contain at least the minimum level of antibodies for diphtheria, which is (b) (4)	(b) (4) (b) (4)	(b) (4) (b) (4)
Diphtheria Toxin Neutralization Potency (b) (4)	(b) (4) (b) (4)	(b) (4)	diphtheria antitoxin antibodies per mL for a product containing a 10% solution of protein..	-----	-----
Appearance: Coloration	(b) (4)	(b) (4)	Specification of colorless to pale yellow (b) (4)	(b) (4)	(b) (4)

Appearance: Clarity and Opalescence	(b) (4) (b) (4)	(b) (4) (b) (4)	(b) (4) (b) (4)	(b) (4) (b) (4)	(b) (4) (b) (4)
Appearance: Visible particles	Visual inspection (b) (4) (b) (4)	Clear and practically free from particles	(b) (4)	Clear and practically free from particles <i>All results complied.</i>	Clear and practically free from particles <i>All results complied.</i>
Extractable volume	(b) (4) (b) (4)	(b) (4) nominal	(b) (4) the label must state the volume in the container. Extractable volume must be equal (b) (4)	(b) (4) nominal <i>All results complied</i>	(b) (4) nominal <i>All results complied</i>
pH	(b) (4)	(b) (4) (4.4-5.2)	(b) (4)	(b) (4) (4.4-5.2) (b) (4)	(b) (4) (4.4-5.2) (b) (4)
Osmolality	(b) (4)	(b) (4) (b) (4)	(b) (4)	(b) (4) (b) (4)	(b) (4) (b) (4)
Total Protein	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

			(b) (4)		
Immunochemical Purity	(b) (4)				
Human IgG		positive	(b) (4)	Positive	Positive
(b) (4)		(b) (4)		<i>All results complied.</i> (b) (4)	<i>All results complied.</i> (b) (4)
				(b) (4)	(b) (4)
Protein Composition (Immunoglobulins)	(b) (4)	(b) (4)	(b) (4)	(b) (4) <i>All results complied.</i> (b) (4)	(b) (4) <i>All results complied.</i> (b) (4)
(b) (4)	(b) (4)				
(b) (4)		(b) (4)	(b) (4)	(b) (4)	(b) (4)
				(b) (4)	(b) (4)
(b) (4)		(b) (4)		(b) (4)	(b) (4)
(b) (4)		(b) (4)		(b) (4)	(b) (4)
(b) (4)		(b) (4)		(b) (4)	(b) (4)
(b) (4)	(b) (4)		(b) (4)		
(b) (4)	(b) (4)	(b) (4)		----	----
(b) (4)	(b) (4)	(b) (4)		----	----
(b) (4)	(b) (4)	(b) (4)		----	----
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	(b) (4)			(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
				(b) (4)	(b) (4)

	(b) (4)			(b) (4)	(b) (4)
Composition of Immunoglobulins	(b) (4)				
IgG		(b) (4)	(b) (4)	(b) (4) 96%	(b) (4) 96%
IgA		(b) (4) 0.3 mg/mL		(b) (4)	(b) (4)
IgM		(b) (4)		(b) (4)	(b) (4)
Anti-A/B Hemagglutinins	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4) (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sterility	(b) (4)	sterile	(b) (4)	Sterile <i>All were sterile.</i>	Sterile <i>All were sterile.</i>
Bacterial Endotoxins	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
*Pyrogens (b) (4)	(b) (4)	(b) (4)	None	Pyrogen-free <i>All were pyrogen-free</i>	Pyrogen-free <i>All were pyrogen-free</i>
Polysorbate 80	(b) (4)	(b) (4) (2-20 µg/mL)	Polysorbate 80 content (b) (4)	(b) (4) (2-20 µg/mL)	(b) (4) (2-20 µg/mL)

			(b) (4)		
Glycine	(b) (4)	(b) (4) (270 - 330 mmol/L)	(b) (4)	(b) (4) (270 - 330 mmol/L)	(b) (4) (270 - 330 mmol/L)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Product Reviewer's Comments: (1) For the majority of the proposed (b) (4) DP specifications, the acceptance criteria appeared to be similar or not significantly different from those set for other licensed IGIV 10% products. Most of the justifications provided by the sponsor appeared to be acceptable. However, there were a few missing specifications (b) (4) and some that needed verification, adjustment or revision (Post-packaging Identity Test, Measles virus neutralization potency, Composition of Immunoglobulins – IgG, IgA, IgM, Antibody to hepatitis B surface antigen).

(2) As mentioned above in Section A, no. 2, there was no (b) (4) specification and test listed in any of the specification tables in the initial BLA submission. After several IRs, the sponsor eventually agreed to implement using a (b) (4) assay and specification of (b) (4) (b) (4) for DP lot release.

(3) As mentioned above in Section A, no. 3, there was also no (b) (4) specification and test listed in any of the specification tables in the initial BLA submission. After three IRs, the sponsor agreed to set the specification for DP lot release as a PMC (see PMC #2e).

(4) As mentioned above in Section A, no. 4, the Identity test (b) (4) initially submitted was discovered to be being performed (b) (4) not at the required post-labeling/post-packaging stage per 21 CFR 610.14. After two IRs, the sponsor agreed to move the Identity test (b) (4) to the post-packaging stage.

(5) As mentioned above in Section A, no. 5, after one IR, the sponsor agreed to round up their Measles Virus Neutralization Potency specification from (b) (4) "CBER Reference Standard" to (b) (4) "CBER Reference Standard".

(6) As mentioned above in Section A, no. 6, after two IRs, the sponsor agreed to revise the unitage of Composition of Immunoglobulins specification from percent (%) to milligrams per mL to match the unitage stated in the package insert and to revise the limits to (b) (4) 0.3 mg/mL IgA, (b) (4) (b) (4) IgG and (b) (4) IgM” as recommended by the Product Office reviewers.

(7) As mentioned above in Section A, no. 7, after one IR, the sponsor agreed to revise their Anti-HBs specification from (b) (4) to (b) (4) as recommended by the Product Office reviewers.

2. Assigned Analytical Procedures and their Validation Studies

In general, all the analytical procedures reviewed here for testing the (b) (4) DP appeared to be suitable for their intended use. The chosen test methods are those typically used by other IGIV manufacturers as well. The sponsor’s Quality Control (QC) test lab and the external test labs validated their test methods appropriately according to (b) (4) guidelines and evaluated almost all of the recommended test parameters. For the tests that were based on (b) (4) methods, only verification was needed (i.e., not a full validation) to demonstrate that Biotest analysts could perform the test as described. The QC test lab was inspected during the Pre-License Inspection (PLI) of the Biotest AG Dreieich facility, which was conducted on December 4-8 and December 11-15, 2023. The PLI outcome of the facility was classified as VAI (Voluntary Action Indicated). The external test labs (b) (4) (b) (4) were not inspected during this current BLA review cycle and were issued inspection waivers instead.

- a. **Anti-HBs** (b) (4) DP (SOP-Q-00591, v.9.0, effective 5-SEP-2023)– The Anti-HBs test is an (b) (4)



Anti-HBs Test Method Validation (VAL-Q-00083_REP-01):



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

(b) (4)

- d. **Measles Virus Neutralization Potency (DP)** (CTM-3466 v.2, approved 28-FEB-2022) –
(b) (4)

(b) (4)

Measles Virus Neutralization Potency (DP) (VIP/00065. v.08. effective 14-DEC-2020).(b) (4)

(b) (4)

Measles Virus Neutralization Potency Test Method Validation (VAL-Q-00044_REP-01, for (b) (4) test only):

(b) (4)

(b) (4)

e. **Polio Virus Neutralization Potency (DP) (CTM-3467 v.2, approved 28-FEB-2022):** (b) (4)

(b) (4)

Polio Virus Neutralization Potency (DP) (VIP/00072, v.4, effective 14-DEC-2020): (b) (4)

(b) (4)

Polio Virus Neutralization Potency Test Method Validation (VAL-Q-00045_REP-01, for (b) (4) test method only):

(b) (4)

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

(b) (4)

h. Identity Test (Post-Packaging Identity Test) (DP) (SOP-Q-00100, v. 6.0, effective 12-OCT-2021) – (b) (4)

[Redacted content]

(b) (4)

Identity Test Method Validation (VAL-Q-00146_REP-01):

(b) (4)

Deviations: No deviations were reported.

i. Appearance (DP)

(1) Coloration (DP) (SOP-Q-00311, v.9.0, effective 24-MAY-2023) – This (b) (4) test method is based on (b) (4)

The coloration of the sample is determined by (b) (4)

(b) (4)


An additional (b) (4) procedure according to (b) (4)

(b) (4)


Coloration Test Method Validation (no report submitted):

(b) (4)

(b) (4)

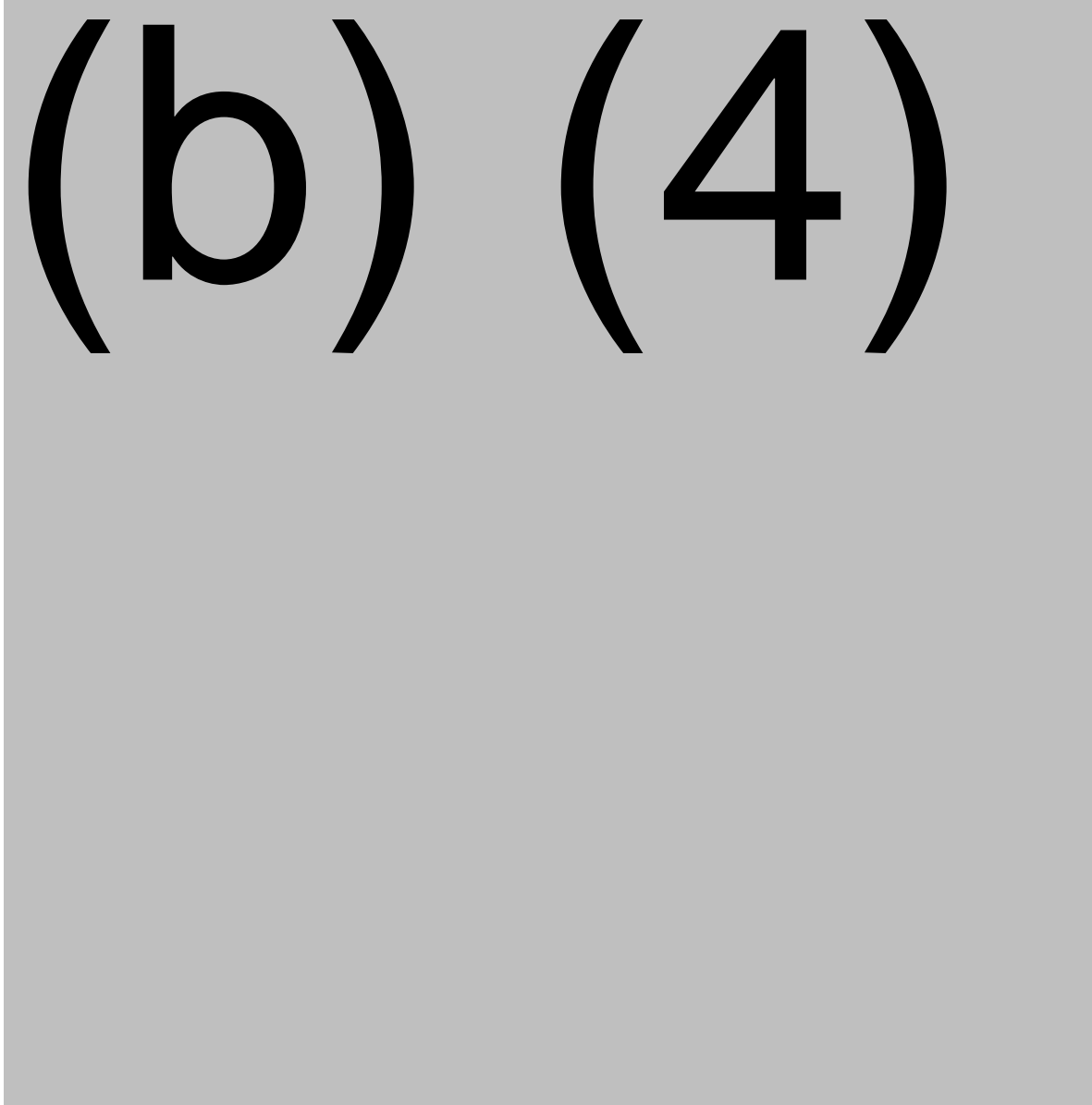


(2) **Clarity and Opalescence** (DP) (SOP-Q-00515, v.2.0, effective 20-AUG-2019) – This
(b) (4)



Clarity and Opalescence Test Method Validation (VAL-Q-00221_REP-01):

(b) (4)



Deviations: No deviations were identified during the verification.

- (3) **Visible Particles** (DP) (SOP-Q-00262, v.5.0, effective 16-JUN-2023) – Visual inspection or the test for the absence of visible particles, suspended particles and defects on the primary packaging material is based on (b) (4)

is performed as a 100% inspection by qualified personnel. (b) (4)

Visible Particles Test Method Validation (no study report submitted):

The sponsor (b) (4)

They confirmed that the test method is suitable for its intended use.

Product Reviewer's Comments: *The Appearance test method SOPs and validation results appeared to be acceptable on paper, however, the manual visual inspection program was found to be inadequate during the PLI of the Biotest AG facility in Dreieich, Germany (see Form FDA 483 issued to Biotest on 15-DEC-2023 and the Establishment Inspection Report dated 21-MAY-2024).* (b) (4)

- j. **Extractable Volume** (DP) (SOP-Q-00197, v.4.0, effective 15-MAY-2023) – Test is based on (b) (4)

Extractable Volume Test Method Validation (no study report submitted):

The sponsor (b) (4)

They confirmed that the test method is suitable for its intended use.

- k. (b) (4)

(b) (4)

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

(b) (4)

3. Control of Materials: Plasma Pool

The U.S. Source Plasma starting material is collected from healthy qualified plasma donors at FDA-licensed plasmapheresis centers. Plasma received from qualified suppliers is stored at (b) (4) at an FDA-approved off-site storage facility or at Biotest until required for processing. Plasma may be stored for a maximum of (b) (4) after donation. Biotest confirms that each batch of final product can be traced to the single plasma donation used for its manufacture and vice versa (from donor to patient and reverse).

Prior to shipment to Biotest or their FDA-approved storage facility, each plasma unit is tested and must be found negative for HBsAg, HIV-1/2 antibody and HCV antibody. In addition, a serological test for syphilis is performed according to 21 CFR 640.65. The plasma units are also tested in (b) (4) which must be found non-reactive for HAV RNA, HBV DNA, HCV RNA and HIV RNA and not more than the defined cut-off limit for Parvovirus B19 DNA as determined by NAT.

Plasma manufacturing pools used in the production of YIMMUGO have a volume of (b) (4) (b) (4)

Table 5 below lists the specifications of the plasma pool and the corresponding serological and (b) (4) tests performed by Biotest at their Dreieich facility.

Table 5: Proposed Specifications for the Plasma Pool

Test	Requirement	Method SOP	Validation Report
Total Protein	(b) (4)	(b) (4)	No report provided
Protein Composition	(b) (4)		No report provided
Anti-HIV	Negative		AB:Q-00144
HBsAg	Negative		AB:Q-00143
HCV RNA	Not reactive		VAL-Q-00100_REP-01
HBV DNA	Not reactive		VAL-Q-00100_REP-01
HIV-1 o/m/-2 RNA	Not reactive		VAL-Q-00100_REP-01
HAV RNA	Not reactive		VAL-Q-00101_REP-01
Parvovirus B19 DNA	(b) (4)		VAL-Q-00101_REP-01

Product Reviewer's Comments: The serological and NAT methods that Biotest uses for testing for bloodborne pathogens in the plasma pool are acceptable and suitable for use, as these are also widely used by other IGIV manufacturers. Their acceptance criterion of $\leq 10,000$ IU/mL Parvovirus B19 DNA complies with the maximum limit for the parvovirus B19 viral load in the manufacturing pool as recommended in the FDA CBER Guidance for Industry: Nucleic Acid Testing (NAT) to Reduce the Possible Risk of Human Parvovirus B19 Transmission by Plasma-Derived Products (dated July 2009).


Serological and NAT Tests for Bloodborne Pathogens in the Plasma Pool

a. **Anti-HIV** (Plasma pool) (SOP-Q-00400, v.4.0, effective 13-JUL-2023) - (b) (4)



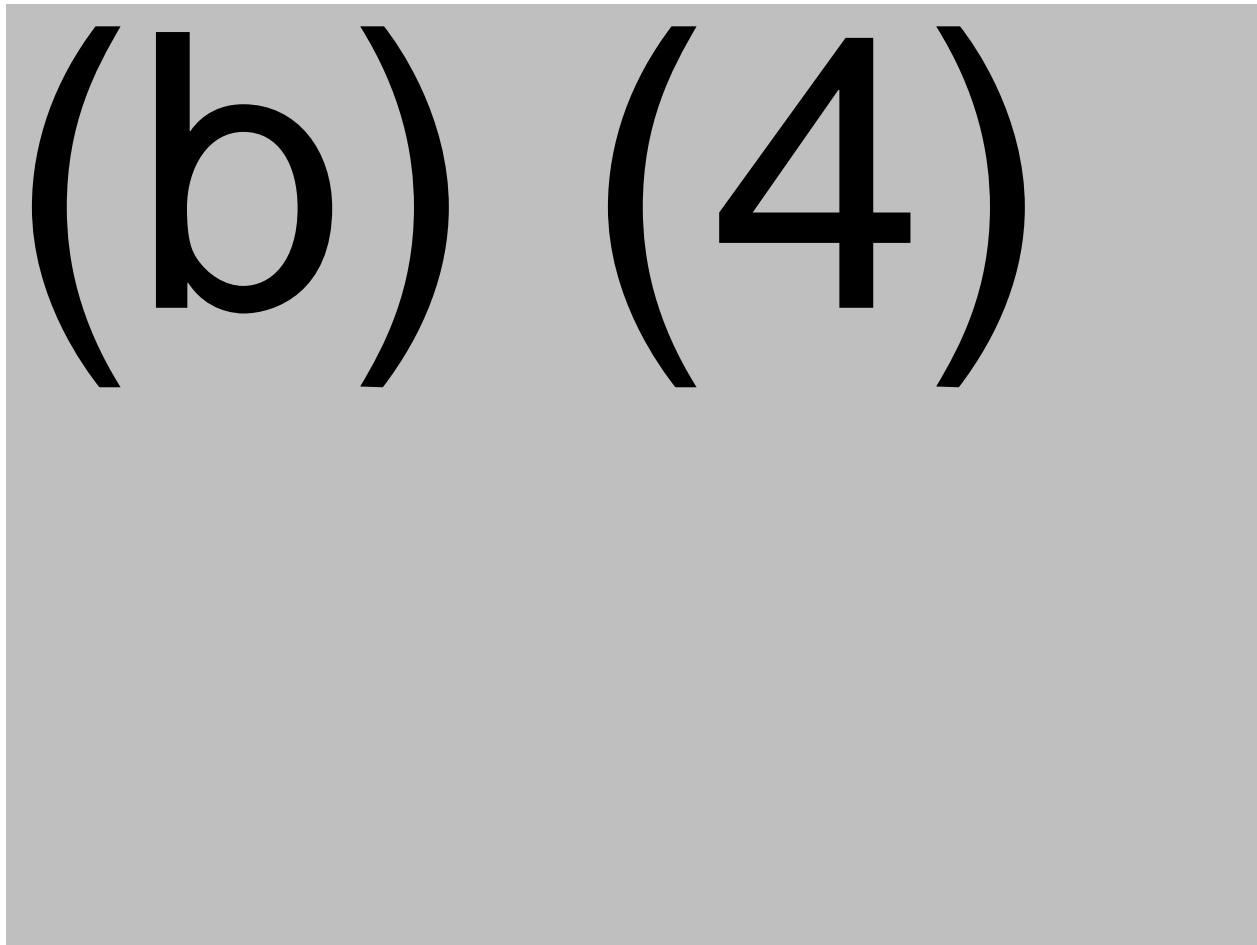
1 page has been determined to be not releasable: (b)(4)

b. **HBsAg** (Plasma pool) (SOP-Q-00398, v.4.0, effective 13-JUL-2023) – (b) (4)



HBsAg Test Method Validation (AB:Q-00143/00):

(b) (4)



(b) (4)

- c. **HCV RNA, HBV DNA, HIV-1/2 RNA (Plasma pool)** (SOP-Q-000494, v.1.0, effective 05-MAY-2021) – (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

HIV-1 RNA Test Method Validation (VAL-Q-00100_REP-01)

(b) (4)


(b) (4)

Product Reviewer's Comments: Biotest's validation data for the (b) (4) test appeared to be acceptable. They were able to demonstrate that their (b) (4) can detect simultaneously several of the known genotypes of HCV and HBV, as well as the known subtypes of HIV-1 and HIV-2 in plasma samples. No deviations were reported.


- d. **HAV RNA, Parvovirus B19 DNA** (Plasma pool) (SOP-Q-000495, v.1.0, effective 05-MAY-2021) – (b) (4)

(b) (4)

(b) (4)

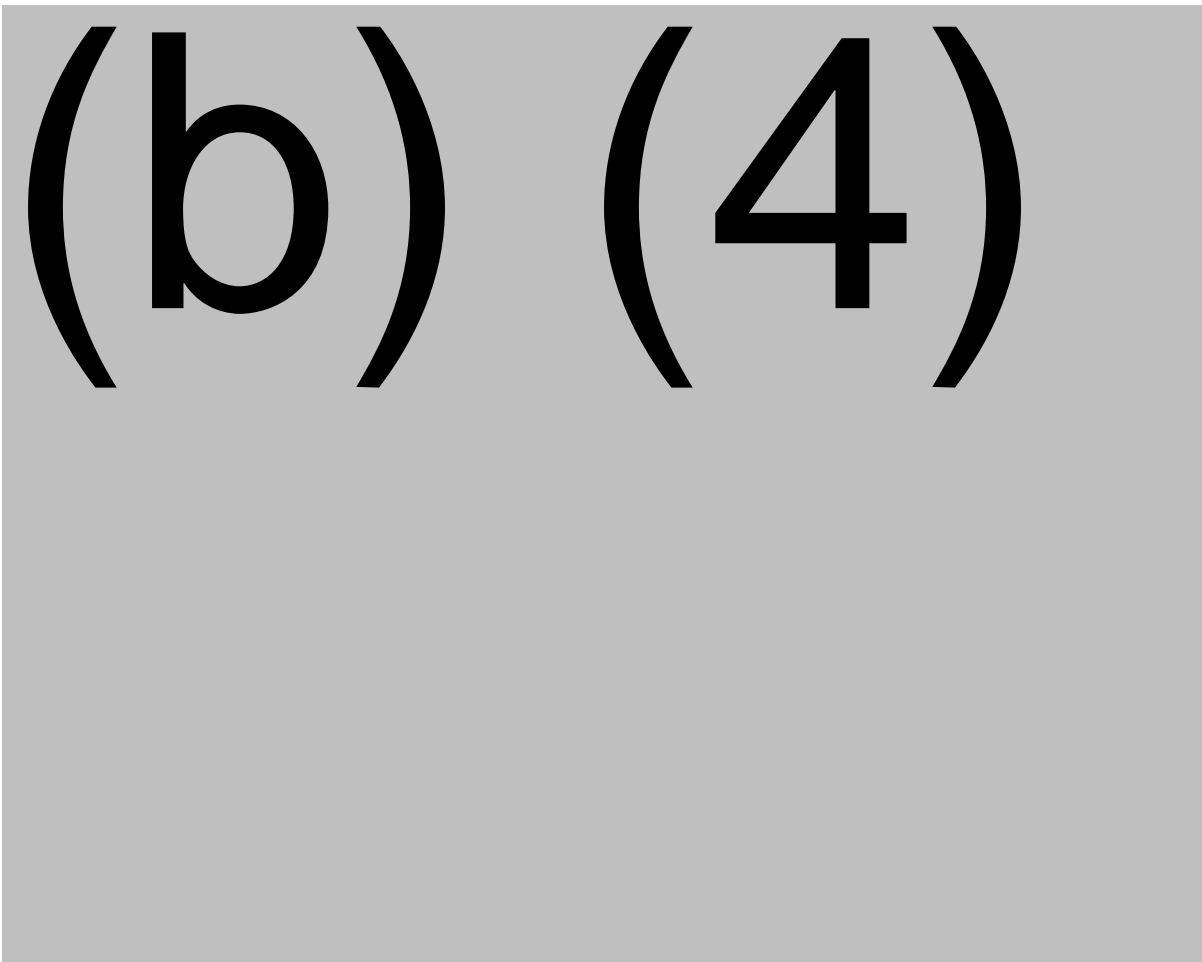
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(b) (4)

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HAV RNA Test Method Validation (VAL-Q-00101_REP-01)

(b) (4)

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(b) (4)

Parvovirus B19 DNA Test Method Validation (VAL-Q-00101_REP-01)

(b) (4)

Product Reviewer's Comments: *Biotest's validation data for the (b) (4) test appeared to be acceptable and showed their ability to detect simultaneously the different HAV and Parvo B19 genotypes in plasma samples. More importantly, Biotest was able to comply with*

the 2009 FDA CBER guidance requirements for Parvo B19 NAT by demonstrating that their (b) (4) assay could detect (b) (4) Parvo B19 genotypes and could accurately quantitate and differentiate a (b) (4) Parvo B19 DNA sample from the other concentrations above and below this concentration, which is the cut-off limit or maximum allowable Parvo B19 viral load in the manufacturing pool. No deviations were reported.

APPENDIX

1. Dr. Yonggang Wang's hemolytic activity test results of DP lots using an in-house complement-based hemolysis assay (Power Point slide presentation for Blood Cluster EMA-FDA-HC: "Hemolysis with reference to Biotest CMC Observations", dated 8-MAR-2024)

REFERENCES

1. Romberg, V., Hoeffler, L., El Menyawi I. Effects of the manufacturing process on the anti-A isoagglutinin titers in intravenous immunoglobulin products. Transfusion 2015 Jul; 55 Suppl 2: S105-9. Doi: 10.1111/trf.13115.
2. FDA CBER Guidance for Industry: Nucleic Acid Testing (NAT) to Reduce the Possible Risk of Human Parvovirus B19 Transmission by Plasma-Derived Products (dated July 2009).