



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

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Subject: Original BLA 125822/0 CMC Review
Product: Immune Globulin Intravenous (Human-pfki), 10% Solution (Qivigy)
Submission Date: September 26, 2024
Sponsor: Kedrion S.p.A.

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Regulatory Milestones

Milestone	Date
DCC Receipt Date	September 26, 2024
Filing Meeting	November 15, 2024
External Mid-Cycle Meeting	March 24, 2025
Pre-Licensure Inspection	April 1-10, 2025
External Late-Cycle Communication	June 11, 2025
Action Due Date	September 25, 2025

Executive Summary

Qivigy (Immune Globulin Intravenous (Human), 10%) is a 10% intravenous immunoglobulin product intended for the treatment of primary humoral deficiency (PI) in patients 18 years of age and older. The product is reviewed under BLA 125822, which was submitted on September 26, 2024, and assigned a standard 12-month review period. Qivigy is manufactured from (b) (4), originating from large pools of human plasma collected at FDA-approved centers. (b) (4) cold ethanol fractionation of the (b) (4) is conducted at Kedrion's (b) (4) facility (Kedrion Biopharma Inc.) using the licensed process described in Biological License Application (BLA) STN (b) (4). The (b) (4) to Kedrion S.p.A.'s facility in Bolognana, Italy (BOL) where it is (b) (4) to the manufacturing facility at (b) (4) where further processing takes place. At (b) (4) the drug substance is manufactured via caprylic acid precipitation and chromatography steps. (b) (4) drug substance is shipped to BOL for sterile filtration and filling. Qivigy is supplied in type (b) (4) glass vials of 50 and 100 mL sizes. Kedrion's clinical trial was carried out with 10% intravenous immunoglobulin manufactured at smaller scale at a contract facility, (b) (4)

(b) (4). The Process Performance Qualification (PPQ) campaign at (b) (4)/BOL included (b) (4) commercial-scale lots covering worst-case manufacturing conditions. The firm's comparability data analysis successfully bridged the clinical trial material with the commercial product manufactured at increased scale.

The primary evidence of safety and efficacy was provided by trial KIG10_US3_PID01, a phase 3, open-label, prospective multicenter study conducted at 11 sites in the United States evaluating the rate of serious bacterial infections (SBIs). The study evaluated 47 patients with PI, of whom 23 were included in pharmacokinetic analyses. Study participants received doses of Qivigy from 200 to 800 mg/kg body weight (bw) every 3 or 4 weeks for a treatment period of approximately 12 months. The pre-specified primary efficacy analysis threshold was met as the annualized SBI rate was less than one SBI per person-year. The PK data and secondary outcomes (incidence rate and duration of infections other than SBIs, hospitalizations, missed school/work) were overall supportive of the product's efficacy.

Recommendation: Approval

Background

Qivigy is intended as replacement immunoglobulin therapy in patients with primary immunodeficiency (PI), characterized by impaired B-cell immunity and reduced production of protective antibodies in response to pathogenic microorganisms. PI diseases include Severe Combined Immunodeficiency Disease (SCID), X-Linked Agammaglobulinemia (XLA), Common Variable Immunodeficiency Disease (CVID), Hyper-IgM Syndrome, Wiskott Aldrich Syndrome, Chronic Granulomatous Disease (CGD), and IgG Subclass Deficiency. Patients with PI experience recurrent, severe bacterial infections (SBIs), with particular risk of serious respiratory infection. For patients with PI, lifelong immunoglobulin therapy is a standard treatment intended to provide neutralizing antibodies that can prevent and limit infections. Immunoglobulins have demonstrated an acceptable safety profile over decades of use. The class includes a boxed warning for thrombosis and renal dysfunction / failure. Qivigy is not currently marketed for use in any country for any indication.

Letters of Authorization

BLA (b) (4)
Type III DMF (b) (4) Type (b) (4) Glass Containers
Type III DMF (b) (4) Rubber Stoppers
Type III DMF (b) (4) (b) (4) (DS container)
Type III DMF (b) (4) Rubber Stoppers
Type III DMF (b) (4) Type (b) (4) Glass Containers

Pre-BLA Meeting: September 15, 2022

- a) Kedrion completed a tech transfer and manufacturing process scale up from the (b) (4) facility in (b) (4), where clinical trial material was made, to (b) (4) Bolognana sites in Italy, the commercial facilities. Demo (n=(b) (4)) and engineering (n=(b) (4)) batches demonstrated elevated IgA content in commercial-scale (b) (4) DP. The firm's strategy is to demonstrate comparability of PPQ batches with clinical batches in the BLA.
- b) FDA instructed to the firm to provide all manufacturing changes between clinical and commercial scale, including date of change; testing should include (b) (4), a potency tests, and description of actual

results of tests for qualitative parameters such as appearance testing. (b) (4) can be used as an alternative to (b) (4) testing when matrix issues preclude use of (b) (4) assay.

- c) FDA advised that PQ batches should include a worst-case batch with (b) (4) times, and worst case process parameters. The firm has used DoE approach to define appropriate ranges in downscale, and does not think covering full range of CPPs at commercial scale is necessary. FDA advised that PPQ CPPs should be within clinical material specifications.
- d) FDA advised that adequacy of PPQ data set was a review issue, and additional batches could be requested.
- e) FDA recommended drug specification changes: (b) (4) as a release specification. Proposed specification changes may be altered by FDA based on review of PPQ data.
- f) (b) (4) for quality control of commercial production, as a post-approval change. FDA agreed that a comparability study should be sufficient to cover the change, and the submission category of the comparability report would be determined while review of the BLA is ongoing.
- g) FDA provided extensive comments and advice on validation of pathogen-removal in downscale. The pathogen removal model steps must reflect commercial scale.
- h) For reduction of isoagglutinins in final product, the firm intends to process only plasma with isoagglutinin screening scores of (b) (4) (low donors) and exclude those with (b) (4) agglutination scores. The firm plans to implement an (b) (4) post-approval.

Drug Substance

Manufacturers

Table 1: Sites for Manufacturing and Testing of Drug Substance

Site	Facility (FEI No.)	Responsibilities
Kedrion Biopharma Inc (b) (4)	(b) (4)	Manufacturing and in-process testing (b) (4) Quality Control (QC) testing of (b) (4)
Kedrion (b) (4)	(b) (4)	Drug Substance (DS, (b) (4) manufacturing from (b) (4) controls, In-process control testing, DS QC testing, Stability testing of DS
Kedrion S.p.A. (BOL) Via Provinciale, Bolognana, Lucca 55027, Italy	3008919567	Drug product sterile filtration and fill; Receipt and storage of (b) (4), Assembling of (b) (4), In-process QC testing, DS QC testing, Stability testing of DS
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Manufacturing Process, Materials, Critical Steps

Description of Manufacturing Process

(b) (4)

20 pages determined to be not releasable: (b)(4)

(b) (4)

Drug Product

Manufacturers

Table 13: Sites for Manufacturing and Testing of Drug Product

Site	Facility ID (FEI No.)	Responsibilities
Kedrion S.p.A. (BOL) Via Provinciale, Bolognana, Lucca 55027, Italy	3008919567	Manufacture of final Drug Product (DP), including aseptic filling, low pH treatment, visual inspection, labeling, secondary packaging, storage. In-process QC testing, Release testing on final DP (except for potency tests), Stability testing of DP
Kedrion (b) (4)	(b) (4)	Release testing of final DP (except for potency tests), Stability testing of DP
(b) (4)	(b) (4)	(b) (4) testing of DP
(b) (4)	(b) (4)	Potency testing of DP (b) (4)
(b) (4)	(b) (4)	(b) (4) testing of DP

Control of Drug Product: Specifications

The Drug Product specifications for Qivigy were found to be acceptable after revisions (Table 14). The analytical methods and their validations and/or qualifications reviewed for the Qivigy Drug Substance and Drug Product were found to be adequate for their intended use.

(b) (4) monitoring provides a means to assess product quality consistency, identify potential manufacturing deviations that could impact patient safety, and mitigate the risk of (b) (4) methodology is a more sensitive method (b) (4), the method currently employed by Kedrion. Additionally, this technique can differentiate between various (b) (4). We recommended that Kedrion develop and implement a (b) (4) method for monitoring (b) (4) in QIVIGY and establish an alert limit to facilitate investigation of potential manufacturing issues. Kedrion committed to developing this assay and establishing alert limits based on evaluation of at least (b) (4) lots collected over a minimum (b) (4). This approach will enable investigation of root causes and determination of appropriate corrective and preventive actions when alert limits are exceeded.

Table 14: Qivigy Drug Product Release Specifications

Test	Specification	Method SOP
Visual Appearance (clarity, color, visible particles)	Clear, colorless/ or pale yellow, essentially free of visible particles	Visual inspection, (b) (4)
pH	4.0-4.5	(b) (4)
Osmolality	240 (b) (4) mOsm/kg	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Extractable volume	(b) (4) nominal volume (50 mL or 100 mL)	(b) (4)
IgG Identity	Proteins of origin: Human. The main component of the preparation corresponds to the IgG component of normal human serum	(b) (4)
IgG Content	(b) (4)	(b) (4)
Total Protein Content	(b) (4)	(b) (4)
Hepatitis B Surface Antigen Antibody (HBsAg-Ab)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Sterility	Sterile	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Bacterial Endotoxins	(b) (4)	(b) (4)

(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
IgA	≤ 50 mg/L	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Protein Composition (IgG purity)	≥ 96%	(b) (4)
Haemagglutinins Anti-A	(b) (4)	(b) (4)
Haemagglutinins Anti-B	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Sodium caprylate content	(b) (4)	(b) (4)
Glycine	0.20-0.28 mol/L	(b) (4)

Revisions done for Drug Product Specifications:

- Kedrion agreed to revise the following Drug Product specifications: (b) (4)
- IgG Content test uses a mathematical calculation based on the test results from Total Protein and Protein Composition. Protein Composition is measured by (b) (4) which does not accurately reflect the IgG percentage in Drug Product. Kedrion agreed to commit a PMC to developing a (b) (4) method for protein composition determination for Drug Product. The method standard operating procedure (SOP) and the final validation study report will be submitted as a Prior Approval Supplement (PAS) no later than March 31, 2027.
- Kedrion agreed to raise their proposed HBsAg-Ab specification from (b) (4) per FDA's request.
- Kedrion agreed to delete their proposed (b) (4) specification for (b) (4), since testing for (b) (4) is sufficient to meet the FDA requirement.

Analytical Testing Validation

Majority of the tests are performed by the Kedrion QC laboratories in BOL (b) (4). (b) (4) tests are performed by (b) (4). According to the sponsor, the validations were conducted in accordance with the ICH guideline Q2(R1). All instruments were qualified and calibrated. The following reviews cover only the tests assigned to the Product Office.

- (b) (4)

Stability of Drug Product

Samples of final product vials from PPQ batches were stored in the horizontal position under real-time conditions (5 ± 3 °C) (b) (4) months, and under accelerated conditions (b) (4) months. Testing parameters and results are reported in stability study # **STB-101-R**. The data set supports a drug product shelf life of 36 months storage at 5 ± 3 °C.

Drug Product Shipping Validation

The shipping validation studies for the finished product at temperature of +2 to +8 °C from BOL to the (b) (4)

The validation strategy of these studies was assessed in the Kedrion's Risk Assessment Shipping Validation of Finished Products. (b) (4) shipping validation deviations were reported, investigated and corrective actions were implemented.

Kedrion uses multiple complex shipping routes. The worst-case routes including (b) (4) were investigated and all shipments during the validation studies were conducted under the worst-case conditions.

Investigation of the impact of shipping process on the quality of the product was not included in the provided shipping validation. In a response to the IR (STN 125822/063), Kedrion clarified that a shaking stimulation study to evaluate the impact of vibrational agitation caused by shipping was executed for both 50 mL and 100 mL QIVIGY vials in June 2025 according to (b) (4). QIVIGY samples were tested and placed on the long-term and accelerated stability studies according to the stability protocol "Mechanical stressed stability study on 10% human normal intravenous immunoglobulin drug product" (STS-186-D). Kedrion commits (STN 125822/062) to submit the qualification summary report for the Transport Stimulation (DCT-1427-R) by December 31, 2025, and the Stability Study Report (STS-186-R) by July 31, 2028. Furthermore, Kedrion commits to perform (b) (4) of shipping validation under worst-case conditions as requested in the IR sent August 20, 2025. The final PMC stability study report will be submitted by February 28, 2027. Parameters of the study and the PMC were submitted under STN 125822/063.

Pre-Licensure Inspection

CBER conducted a Pre-License Inspection (PLI) of Kedrion S.p.A. Drug Substance (DS) facility at (b) (4), and a Form FDA 483 with two (2) observations was issued at the conclusion of the inspection. The firm's response to the observations and the corrective actions were reviewed and found to be adequate. The inspection was classified as voluntary action indicated (VAI).

Inspectional Follow-up for (b) (4) Facility

1. Evaluate handwritten entries in batch records to ensure all modifications are properly managed through the change control system and that any deviations are appropriately documented according to established procedures.
2. Verify availability and accessibility of current standard operating procedures (SOPs) at manufacturing locations to ensure personnel have immediate access to required documentation during operations.
3. Review the comprehensiveness and adequacy of root cause investigation processes, assessing whether investigations provide sufficient detail and follow a systematic approach to identify underlying causes.
4. (b) (4) warehouses are located at (b) (4) for storing (b) (4) under "exceptional circumstances." Assess what the "exceptional circumstances" are; evaluate how the (b) (4) stored at these warehouses is tracked; and make sure they are not used to store DS or DP.

CBER conducted a Pre-License Inspection (PLI) of Kedrion S.p.A. Drug Product (DP) facility at Bolognana (BOL), Galliciano, Lucca, Italy facility on April 8-10, 2025. No Form FDA 483 was issued. The inspection was classified as no action indicated (NAI).

Inspectional Follow-up for BOL Facility

1. Evaluate handwritten entries in batch records to ensure all modifications are properly managed through the change control system and that any deviations are appropriately documented according to established procedures.
2. Inspect cold storage equipment (refrigerators (b) (4)) for ice accumulation and verify compliance with preventive maintenance schedules.
3. Assess the completeness and thoroughness of deviation investigations to ensure investigations are conducted according to established protocols.
4. Review visual inspection procedures to confirm that threshold studies have established the minimum detectable particle size that can be consistently and reproducibly identified by qualified inspection personnel.

Post-marketing Commitments (PMC)

1. Kedrion commits to providing validation of (b) (4) as a Post Marketing Commitment (PMC). The validation report will be submitted as a Postmarketing Commitment – Final Study Report by December 31, 2025. Please include the (b) (4) in your final study report.
2. Kedrion commits to performing a concurrent (b) (4) validation (b) (4). The interim results of the studies will be submitted annually in an Annual Report. Kedrion commits to notifying the FDA of any (b) (4)

failures within 45 days of the occurrence, as a Postmarketing Commitment Submission – Status Update. The final validation study reports will be submitted as a Changes Being Effectuated (CBE) supplement no later than December 31, 2026.

3. Kedrion commits to submitting a final validation study report to confirm the proposed maximum (b) (4) as a Changes Being Effectuated (CBE) supplement by December 31, 2026. Kedrion commits to notifying the FDA of any (b) (4) failures within 45 days of the occurrence as a Postmarketing Commitment Submission – Status Update.
4. Kedrion commits to (b) (4) method for (b) (4) for Drug Product. The method standard operating procedure (SOP) and the final validation study report will be submitted as a Prior Approval Supplement (PAS) no later than March 31, 2027.
5. Kedrion commits to submitting stability study data for lots (b) (4) annually as a Post-marketing Commitment Submission-Status Update. Within three months after the completion of the study, a final stability report will be submitted as a Post-marketing Commitment Submission-Final Study Report by June 30, 2027. All stability failures will be reported within 45 days of the occurrence as a Post-marketing Commitment Submission - Status Update.
6. Kedrion commits to evaluate (b) (4). Kedrion proposes to submit data on (b) (4) and the relevant assessment as a PMC by December 31, 2026. Final study report submission: December 31, 2026
7. Kedrion commits to providing the (b) (4) by December 31, 2025. The analytical results for (b) (4) samples will be provided as well in the qualification summary report. Kedrion commits to providing the available results of the long-term (b) (4) months) and accelerated stability study (b) (4) months, completed) for these samples by June 30, 2026. The complete stability results for long term stability study (36 months) these samples will be provided at the end of the study (Reference document STS-186-R, expected due date by 31 July 2028).
8. Kedrion commits to establish a final container action limit for (b) (4) using (b) (4) methodology. These limits will be determined following evaluation of at least (b) (4) lots collected over a (b) (4). When action limits are exceeded, Kedrion commits to investigating root cause and determining corrective and preventative actions as applicable. (b) (4) in final container will be measured and reported for information only. The method procedure for quantitation of (b) (4) will be submitted for evaluation in a Postmarketing Commitment – Status Update by 31 December 2026. The method validation and the action limits for (b) (4) in final container will be submitted as a Prior Approval Supplement Postmarketing Commitment – Final Study Report by December 31, 2027.
9. Kedrion commits to performing an (b) (4) validation under worst-case conditions. A final study report will be submitted as a Post-marketing Commitment Submission-Final Study Report by February 28, 2027. The validation study will include but not be limited to the following information:
 - (b) (4).

