Summary Basis for Regulatory Action

Date:	September 26, 2025
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BLA STN:	125822/0
Applicant:	Kedrion S.p.A.
Submission Receipt Date:	September 26, 2024
Action Due Date:	September 26, 2025
Proper Name:	Immune Globulin Intravenous, human-kthm 10% Solution
Proprietary Name:	QIVIGY
Indication:	Treatment of adults with Primary Humoral Immunodeficiency (PI)

Recommended Action: The Review Committee recommends approval of this product.

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Acting Director, Office of Clinical Evaluation, Office of Therapeutic Products

Discipline Reviews	Reviewer / Consultant - Office/Division
Regulatory	Julia Wright, MHA, RN, CBER/OTP/ORMRR
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Jennifer Reed, PhD, CBER/OTP/OPPT/DPD, Nancy Eller, MHS, CBER/OTP/OPPT/DPD, Olga Simakova, PhD, CBER/OTP/OPPT/DPD, Pei Zhang, MD, CBER/OTP/OPPT/DPD, Maria Virata, PhD, CBER/OTP/OPPT/DPD, Hailing Yan, MS, CBER/OTP/OPPT/DPD, Lilin Zhong, MS, CBER/OTP/OPPT/DPD, Lu Deng, PhD, CBER/OTP/OPPT/DPD, Malgorzata Norton, MS, Yambasu Brewah, PhD, CBER/OTP/OPPT/DPD, Jianping Li, PhD, CBER/OTP/OPPT/DPD, Kam Sang Kwok, PhD, CBER/OTP/OPPT/DPD Lisa Pham, CBER/OCBQ/DMPQ, Erin Hill, CBER/OCBQ/DMPQ George Kastanis, CBER/OCBQ/DBSQC, Anil Choudhary, PhD, CBER/OCBQ/DBSQC, Claire Wernly, PhD, CBER/OCBQ/DBSQC, Emnet Yitbarek, PhD, CBER/OCBQ/DBSQC, Jing Lin, PhD, CBER/OCBQ/DBSQC, Parmesh Dutt, PhD, CBER/OCBQ/DBSQC
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	Sairah Thommi, MD, CBER/OTP/OCE/DCEGM Sarah Frasure, MD, CBER/OBPV/DPV Jennifer Chan, PharmD, CBER/OCBQ/DIS/BMB
Statistical	Triparna Poddar, PhD, CBER/OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office)	Evi Struble, PhD, CBER/OTP/OPPT/DPD
Clinical Pharmacology	Xiaofei Wang, PhD, CBER/OTP/OCE/DCEGM
Labeling • Promotional (OCBQ/APLB) • Regulatory Review	Jun Lee, PharmD/PhD, CBER/OCBQ/DCM/APLB Afsah Amin, MD, MPH CBER/OTP/OCE

Discipline Reviews	Reviewer / Consultant - Office/Division
Other Review(s) not captured above categories, for example: • Consults	Zainab Mansaray-Storms, PhD, CBER/OCBQ/DMPQ Frantisek Bizik, PhD, CBER/ORO/DI/RMB
Advisory Committee Summary	N/A

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1. Introduction

Kedrion S.p.A. submitted a biologics license application (BLA), STN 125822, for licensure of Immune Globulin Intravenous, Human-kthm, 10% Solution with the

proprietary name of QIVIGY, to treat adults with primary humoral immunodeficiency (PI). The submission was reviewed under standard review clock.

QIVIGY is a 10% solution intravenous immunoglobulin product. It is manufactured from (b) (4) at Kedrion S.p.A's facility at (b) (4) via caprylic acid precipitation and chromatography steps. (b) (4) drug substance is shipped to Kedrion's Bolognana, Italy facility (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). The firm's comparability data analysis successfully bridged the clinical trial material with the process performance qualification batches manufactured at increased scale.

The primary evidence of safety and effectiveness 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 adult patients with PI, of whom 23 were included in pharmacokinetic analyses. Study participants received doses of QIVIGY from 266 to 826 mg/kg body weight (bw) every 3 or 4 weeks for a treatment period of approximately 12 months. In alignment with the Agency's guidance "Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous, Human as Replacement Therapy for Primary Humoral Immunodeficiency" (2008), 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. No deaths occurred in the study, and no serious adverse events were related to the product. The most commonly reported adverse reactions were headache, fatigue, nausea, infusion-related reactions, positive direct Coombs test, sinusitis, dizziness, and diarrhea.

The review team recommends traditional approval for QIVIGY for the treatment of adults with Primary Humoral Immunodeficiency with pediatric studies to be completed as a post marketing requirement (PMR), and product / facility related updates and corrections to be completed as post marketing commitments (PMCs).

Acknowledging the critical importance of immune globulin intravenous (IGIV) products in treatment of PI, the Agency has exercised regulatory flexibility in review of this BLA to ensure product availability for patients. The Applicant's commercial process includes several steps (e.g. chromatography, filtration) for which the provided validation did not cover the proposed lifetime of use. To fill the validation gaps, the Applicant submitted study protocols which will be completed after approval with final study reports submitted as PMCs. Similarly, several gaps in testing validation will be bridged with approved study protocols to be completed post- approval, with submission of final study reports set as PMCs. The Applicant's worst-case shipping validation studies will be expanded, extrapolating from real-world and modeling studies, and will be completed post-approval with the submission of a final study report, as a PMC. Final stability study information for the process performance qualification (PPQ) lots will be submitted as a PMC. The Applicant's leachables study for final product containers was carried out under exaggerated conditions, and identified a small increase in elemental (b) (4), judged not

to be clinically significant. The Applicant agreed to a GMP-focused study post-approval to determine the range of elemental (b) (4) in the first (b) (4) lots of (b) (4) product, and to provide data in tandem with strategies to remove this impurity if needed, as a PMC final study report. Finally, the follow up for corrective actions proposed during the Applicant's prelicensure inspection (e.g. equipment maintenance procedure, documentation and management of deviations) will be deferred to the next routine facility inspection. All the above post marketing commitments could have been dealt with premarketing and likely would have led to non-approval or a delay in approval. By exerting regulatory flexibility FDA facilitated approval on the action due date.

Considering the importance of ensuring that children have access to these therapies and our current knowledge of this disease and similar immunoglobulin products (including similarities in disease manifestations between adult and pediatric patients, expectations that efficacy in the pediatric population will be similar to that observed in the adult population, and a well-characterized safety profile among other intravenous immunoglobulin commercial products to treat both adult and pediatric populations), the FDA exerted regulatory flexibility in the requested number of pediatric patients and duration of follow-up previously agreed to for fulfillment of the Pediatric Research Equity Act (PREA) post marketing requirement (PMR). Additional extrapolation from pharmacokinetic data will allow product availability sooner for the pediatric population.

2. Background

QIVIGY is intended as replacement immunoglobulin therapy in patients with PI, a form of primary immunodeficiency characterized by impaired B-cell immunity and reduced production of protective antibodies in response to pathogenic microorganisms. PI diseases include, but are not limited to, congenital agammaglobulinemia, severe combined immunodeficiency, X-linked agammaglobulinemia, common variable Immunodeficiency (CVID), and Wiskott Aldrich syndrome,. Patients with PI are at increased risk of recurrent, severe bacterial infections (SBIs), with particular risk of serious bacterial pneumonia. The standard of care treatment includes lifelong immunoglobulin therapy that provides antimicrobial antibodies that can prevent and limit infections. In general, immunoglobulin products have similar safety profiles established over decades of use, with all immunoglobulin product labels including a boxed warning for thrombosis and renal dysfunction / failure.

QIVIGY is not currently marketed for use in any country for any indication at the time of this licensure.

Table 1. Regulatory History.

Regulatory Events / Milestones	Date
1. Pre-IND meeting	PS003227 May 12, 2017
2. IND submission	18648 December 04, 2018
3. Pre-BLA meeting	August 16, 2022
4. BLA 125822/0 submission	September 26, 2024
5. BLA filed	November 25, 2024
6. Mid-Cycle communication	March 28, 2025
7. Late-Cycle meeting	June 11, 2025, canceled by Applicant
8. Action Due Date	September 26, 2025

3. Chemistry Manufacturing and Controls (CMC)

c. Product Quality

QIVIGY is a liquid formulation of 10% human IgG. Kedrion's (b) (4) facility (Kedrion Biopharma Inc.) prepares (b) (4) via (b) (4) ethanol fractionation of large pools of (b) (4) Plasma, collected only at FDA-licensed facilities. (b) (4) is shipped (b) (4) to Kedrion's BOL facility, which receives, assembles, and delivers (b) (4) for further processing. At (b) (4) is solubilized and subjected to 2 sodium caprylate treatments steps with (b) (4) filtration to remove precipitated proteins and viruses. Diluted filtrate is subjected to anion exchange chromatography, followed by nanofiltration as an orthogonal viral removal step. The nanofiltrate is ultrafiltered and diafiltered to adjust concentration and pH prior to formulation with glycine. The (b) (4) in type (b) (4) glass vials with nominal fill volumes of 50 or 100 ml. The product is incubated in final container at the low pH of 4.0-4.5 as an additional virus reduction step.

The overall capacity for virus inactivation and removal was evaluated with spiking studies at the laboratory scale, using a validated model of the manufacturing process and relevant model viruses: HIV-1; Bovine Viral Diarrhea virus (BVDV) as a model for hepatitis C virus; Pseudorabies virus (PsRV) as a model for large enveloped DNA viruses such as Herpes and Hepatitis B viruses; Hepatitis A virus; Encephalomyocarditis virus (ECMV) as a model for hepatitis A virus; Porcine Parvovirus (PPV) as a model for Parvovirus B19. Logarithmic reduction factors (LRFs) reflecting individual process steps and across the entire manufacturing process are reported in Table 2.

Table 2: Viral Inactivation / Removal Capacity of the QIVIGY Manufacturing Process

Process Step	BVDV	HIV-1	PsRV	HAV	PPV	EMCV
1st Caprylate	3.35	NI	NI	>5.93	2.69	NI
2nd Caprylate	>5.37	>4.54	>6.79	NA	NA	NA
Nanofiltration	>5.26	2.27	NI	>4.85	>6.19	>4.28
Inactivation Low pH	2.45	6.17	6.65	NI	NI	3.43
Overall Viral Reduction	>16.43	>12.98	>13.44	>10.78	>8.88	>7.71

Published data indicate that immunoglobulin products purified via caprylate / chromatography methods can contain higher levels of hemagglutinating antibodies associated with hemolytic adverse events. Kedrion successfully addressed this risk by selecting anti-A/B low (b) (4) Plasma for the preparation of (b) (4) . In addition, Kedrion plans to add an (b) (4) to (b) (4) in the QIVIGY manufacturing process, as a post-marketing change.

As part of an extensive extractables and leachables evaluation, Kedrion reported elemental (b) (4) as a leachable, possibly originating from the stopper. While not identified as a safety issue, Kedrion agreed as a GMP-related PMC to evaluate sources of (b) (4) in the manufacturing process and devise a strategy to reduce this impurity in the final container.

d. Testing Specifications

The Drug Product specifications for QIVIGY were found to be acceptable after revisions (Table 3). 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.

Table 3: QIVIGY Drug Product Release Specifications

Determination	Requirement	Method
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)

Determination	Requirement	Method
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)
(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)
IgA	≤ 50 mg/L	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Protein Composition (IgG purity)	≥ 96%	(b) (4)

Determination	Requirement	Method
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)

e. CBER Lot Release

The lot release protocol template was submitted to CBER for review and was found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

a. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of Immune Globulin Intravenous, Human–kthm, 10% solution (QIVIGY) are listed in Table 4 below, in addition to the activities performed and inspectional histories.

Table 4: Manufacturing Facilities Table for Immune Globulin Intravenous, Human-kthm 10% Solution (QIVIGY)

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification/ Results
Facility: Kedrion (b) (4). (referred as to Kedrion (b) (4) DP release and stability testing; DS manufacturing ((b) (4) , quality control, and stability testing	(b) (4)	(b) (4)	PLI	CBER/DMPQ (b) (4) VAI

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification/ Results
Facility: Kedrion S.p.A. Via Provinciale Bolognana, Lucca 55027 Italy DP manufacturing, (b) (4), release, and stability testing	3008919567	339096023	PLI	CBER/DMPQ April 2025 NAI
Facility: Kedrion Biopharma Inc. (KBI) (b) (4) DS manufacturing (b) (4)	3003683714	080452111	Waiver	ORA/OBPO March 2024 VAI
Facility: (b) (4) DP release testing	3010167002	277961392	Waiver	ORA/OBPO (b) (4) NAI
Facility: (b) (4) DP release testing	(b) (4)	(b) (4)	Waiver	(b) (4) VAI
Facility: (b) (4) DP release testing	(b) (4)	(b) (4)	Waiver	(b) (3), (b) (4) VAI

(b) (3), (b) (4) Drug Product (DP); Drug Substance (DS); (b) (4) ; No Action Indicated (NAI); Office of Biological Product Operations (OBPO); Office of Regulatory Affairs (ORA); Pre-license Inspection (PLI); Voluntary Action Indicated (VAI)

CBER/DMPQ conducted a PLI at Kedrion (b) (4) for the DS manufacturing and DP release testing. A Form FDA 483 was issued. The firm adequately responded to the observations. All inspectional issues were resolved, and the inspection was classified as VAI.

CBER/DMPQ conducted a PLI at Kedrion BOL in April 2025 for the DP manufacturing, fill/finish, labeling and packaging activities. No objectionable issues were identified, and the inspection was classified as NAI.

ORA/OBPO conducted a surveillance inspection at Kedrion Biopharma Inc. in March 2024, and a Form FDA 483 was issued. The firm adequately responded to the observation. All inspectional issues were resolved, and the inspection was classified as VAI.

ORA/OBPO conducted a surveillance inspection at (b) (4) and the inspection was classified as NAI.

(b) (4) conducted a surveillance inspection at (b) (4). The firm responded to the identified deficiencies and a GMP certificate was issued. ORA reviewed the inspection outcome through the mutual recognition agreement (MRA) and concluded the inspection is equivalent to a VAI classification.

(b) (3), (b) (4) conducted a surveillance inspection at (b) (4). The firm responded to the identified deficiencies, and a GMP certificate was issued. ORA reviewed the inspection outcome through the MRA and concluded the inspection is equivalent to a VAI classification.

b. Container Closure System

The container closure system for QIVIGY consists of Type (b) (4) glass vials available in 50 mL and 100 mL sizes, sealed with stoppers and secured using an over-seal featuring a plastic flip-off cap. The primary packaging components used for QIVIGY are described in Table 5 below. The primary components are sterilized before use.

Kedrion S.p.A. conducted the container closure integrity testing (CCIT) employing (b) (4) method; all acceptance criteria were met.

Table 5: Container Closure System for QIVIGY

Component	Description	Manufacturer
Drug product container	50 mL and 100 mL Type (b) (4) molded colorless and transparent glass vials	(b) (4)
Drug product closure	20 mm halobutyl rubber stopper, grey	(b) (4)
Drug product closure	Polypropylene flip-off top cap, transparent	(b) (4)

c. Environmental Assessment

A categorical exclusion from Environmental Assessment / Environmental Impact Statement was requested by the Applicant under 21 CFR 25.31. FDA concluded that the request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

The ability of antibodies in QIVIGY to opsonize (b) (4) bacteria and promote neutrophil phagocytosis was evaluated along with two commercial IGIV products. The study was performed under Good Laboratory Practices (GLP) conditions and confirmed functionality of antigen binding (Fab) and effector function (Fc) regions of antibacterial antibodies in QIVIGY. This study demonstrated the potential of QIVIGY to neutralize two pathogens relevant to the PID indication at similar levels as other commercial IGIV products.

An acute, single intravenous dose GLP study was performed in (b) (4) rats to assess potential toxicity and compare the pharmacokinetic and toxicokinetic profile of QIVIGY with a reference commercial IGIV product. Animals were assessed 1 and 14 days following administration of 1 or 2 g/kg IGIV for measures of systemic and local toxicity. The pharmacokinetic and safety profiles of the two tested immunoglobulin treatments were similar, with no unexpected toxicities observed.

Toxicity of the excipient glycine and impurity sodium caprylate was assessed via literature review. No safety concerns related to potential toxicity of excipients or impurities in QIVIGY were identified.

There were no nonclinical pharmacology or toxicology related issues that would preclude approval of QIVIGY.

5. Clinical Pharmacology

The clinical pharmacology of QIVIGY was evaluated in a Phase 3, open-label, prospective, multicenter study (Study KIG10_US3_PID01).

The pharmacokinetic (PK) analysis of QIVIGY was assessed in 23 adult patients (5 patients for the 3-week dosing schedule and 18 patients for the 4-week dosing schedule) in Study KIG10_US3_PID01. Serum concentrations of total IgG were measured in 23 subjects following the 5th infusion of QIVIGY for patients on the 4-week dosing schedule, or the 7th infusion for patients on the 3-week dosing schedule. The dose of QIVIGY used in these subjects ranged from (b) (4) mg/kg to 826 mg/kg.

Following the administration of QIVIGY, serum concentrations of total IgG increased rapidly before gradually declining and had returned to close to their baseline levels by the end of the dosing interval for both dosing regimens. For baseline-uncorrected total serum IgG versus time profiles, the mean C_{max} (mean±SD) for patients on the 21-day infusion schedule was 2680±282 mg/dL, and for patients in the 28-day schedule it was 2300±466 mg/dL. The respective C_{min} (mean±SD) were 1140±150 and 994±200 mg/dL. The estimated mean serum half-life for uncorrected total IgG was 24.5 days (587 h) for patients on the 21-day infusion schedule and 37.3 days (896 h) for patients on the 28-day schedule.

The total IgG trough levels were generally maintained, and no trend was observed during the study. The mean (range) of baseline total IgG trough levels were 10.1 (5.2 to 12.2) g/L and 10.4 (6.4 to 27.4) g/L for 3-week and 4-week dosing schedule, respectively. The mean (range) of total IgG trough levels at study termination visit were 11.4 (9.0 to 14.5) g/L and 10.3 (7.2 to 17.0) g/L for 3-week and 4-week dosing schedule, respectively.

The pattern of serum levels versus time profiles for IgG subclasses (IgG1, IgG2, IgG3, and IgG4) matched with total IgG levels. All the mean values of IgG subclasses (IgG1, IgG2, IgG3, and IgG4) were maintained within the normal reference ranges.

In general, the IgG-specific antibody serum levels followed an overall similar pattern as that of total IgG and were considered protective.

6. Clinical/Statistical

a. Clinical Program

The primary evidence of safety and efficacy for this BLA is from a Phase 3, open-label, prospective, single-arm, multi-center study conducted in the U.S. under IND 18648 comparing annualized rate of SBI to historical standards. The study design is consistent with the FDA guidance for studies supporting marketing applications for intravenous immunoglobulin therapies for the treatment of PI.

The study planned to enroll 50 patients who were 2 to 70 years of age, had received stable doses of IGIV therapy for at least 3 infusion cycles, and had therapeutic IgG trough levels (≥ 6 g/L at 2 infusion cycles within 12 months). Patients were to receive the same dose and treatment interval as per their previous IGIV treatment (protocol specified doses were to be 200-800 mg/kg every 3 or 4 weeks) for a treatment period of approximately 12 months.

The primary efficacy endpoint was annualized rate of acute serious bacterial infections (SBI), defined as bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, visceral abscesses, or bacterial meningitis. Secondary efficacy analyses included maintaining IgG trough levels above 6 g/L, IgG subclass (IgG1, IgG2, IgG3, IgG4) levels, specific antibody levels (anti-tetanus, anti-pneumococcal capsular polysaccharide, anti-*Haemophilus influenza*, and anti-measles), occurrence of any infection other than acute SBIs, occurrence and length of fevers, occurrence and duration of hospitalizations, occurrence and duration of antibiotic treatments, missed days of school/work/major activities due to infection, and a quality of life assessment.

Of 59 enrolled patients, 47 were eligible and received QIVIGY. All 47 adult patients completed the study. The median age was 56 years (range: 20 to 70 years). Although pediatric patients were eligible for enrollment, enrollment numbers were achieved with adult patients prior to enrollment of any pediatric patients. Therefore, no children were enrolled. Most patients were white (n=45; 95.7%) and female (n=30; 63.8%). The most common underlying cause of PI was common variable immunodeficiency (n=34; 72.3%).

During the study, patients received QIVIGY doses between 266 to 826 mg/kg every 3 or 4 weeks, for a treatment period of approximately 12 months. Infusions were initiated at a rate of 1 mg/kg/minute for 30 minutes. If tolerated, the rate was increased at 30-minute

intervals to a maximum of 8 mg/kg/minute. Two patients were treated with doses outside the planned ranges. No adverse events were assessed as related to the increased doses. Doses were adjusted as necessary for changes in body weight or to maintain targeted IgG levels.

No acute SBIs occurred during the study, yielding an estimated incidence rate of 0 acute SBIs per person-year. The associated upper bound of the one-sided 99% confidence interval was <1, meeting the study success threshold recommended in FDA's *Guidance for Industry: Safety, Efficacy, and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-efficacy-and-pharmacokinetic-studies-support-marketing-immune-globulin-intravenous-human)*. There were 98 infections other than acute SBIs (with a median duration of 12 days) that occurred in 36 (77%) patients, yielding an incidence rate of 2.1 per person-year. There were no patients hospitalized due to infection.**....**
The safety population set included all patients who received at least one dose of QIVIGY (n=47). A total of 643 infusions of QIVIGY were administered. No deaths were reported. Four patients reported serious adverse events (depression, hypotension, hyperglycemia, acute cholecystitis, and osteoarthritis) that were adjudicated by the review team as unrelated to the product. The most commonly (occurring in >5% of patients) reported adverse reactions (including adverse events within 72 hours of an infusion and any causally related event) were headache, fatigue, nausea, infusion-related reactions, positive direct Coombs test, sinusitis, dizziness, and diarrhea.

Based on the clinical and clinical pharmacology data included in the BLA, there is a favorable benefit-risk profile to support approval of QIVIGY for the treatment of adults with PI.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspection assignments were issued for the Applicant and three domestic clinical study sites that participated in the conduct of Protocol KIG10-US3-PID01. The inspections did not reveal significant issues that impacted the data submitted in this original Biologics License Application (BLA).

c. Pediatrics

No pediatric patients were enrolled in the study. The safety, efficacy, and PK data for children 2 to <17 years of age are being assessed in an ongoing deferred pediatric study as part of a PREA post-marketing requirement (PMR). The pediatric study requirement for age 0 to <2 years is waived as PI is rarely diagnosed in this age group, and therefore conducting studies in this age group is impossible or highly impractical.

d. Other Special Populations

No other special populations were assessed in the study.

7. Safety and Pharmacovigilance

Pharmacovigilance Plan

The Applicant submitted a pharmacovigilance plan for QIVIGY. The important identified risk associated with QIVIGY includes risk of hypersensitivity reactions, including anaphylaxis. Important potential risks include hemolytic anemia, thromboembolic events, renal dysfunction, acute renal failure, aseptic meningitis syndrome, hemolysis, transfusion-related acute lung injury, and transmissible infectious agents. OBPV/DPV recommends the following for postmarketing safety monitoring of QIVIGY:

Routine pharmacovigilance, which includes adverse event reporting in accordance with 21 CFR 600.80.

The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related postmarketing requirement (PMR), and there is no agreed upon safety-related postmarketing commitment (PMC) at this time.

8. Labeling

The proposed proprietary name, QIVIGY, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on December 9, 2024, and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on December 18, 2024.

The APLB review addresses the proposed prescribing information and the proposed package and container labels, submitted on September 26, 2024.

The Office of Clinical Evaluation (OCE) labeling review team, together with the relevant discipline review teams, reviewed and revised the proposed prescribing information to ensure that it meets regulatory/statutory requirements, is consistent with current labeling practice, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the product, and provides clear and concise information for the healthcare providers. With the agreed revisions, the prescribing information is acceptable.

9. Advisory Committee Meeting

This application was not referred to an Advisory Committee because our review of information submitted in the BLA, including manufacturing, clinical study design, and trial results did not raise regulatory concerns or unresolved scientific issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of this BLA.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The review committee recommends traditional approval of QIVIGY for the treatment of adults with primary humoral immunodeficiency (PI).

b. Benefit/Risk Assessment

Data submitted in the BLA provide substantial evidence of effectiveness and safety in adults with PI. QIVIGY is effective in reducing the number of SBIs to less than one per patient-year in adults with PI. The most commonly reported adverse reactions (including adverse events within 72 hours of an infusion and any causally related event) were headache, fatigue, nausea, infusion-related reactions, positive Coombs direct testing, sinusitis, dizziness, and diarrhea. Adverse reactions were consistent with those anticipated for this class of medications. For immunoglobulin therapy for PI, the Agency accepts a single adequate and well-controlled (AWC) study with confirmatory data from other AWC studies within the class for the same indication. Overall, the benefit-risk profile for adults with PI treated with QIVIGY is favorable.

c. Recommendation for Postmarketing Activities

The Applicant will conduct routine pharmacovigilance with adverse event reporting in accordance with 21 CFR 600.80. The available safety data do not substantiate a need for a postmarketing commitment safety study or a Risk Evaluation and Mitigation Strategy (REMS). Therefore, there is no agreed-upon post marketing commitment safety study for this product. However, additional post marketing studies were deemed necessary and are listed below.

1. Deferred pediatric study under PREA for the treatment of primary immune deficiency in pediatric patients ages 2 years to less than 17 years.

   Final Protocol Submission: December 30, 2025

   Study/Trial Completion: April 30, 2026

   Final Report Submission: July 30, 2026

The Applicant has agreed to the following Post Marketing Commitments (PMCs):

2. 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.

   Final Study Report Submission: December 31, 2025

3. Kedrion commits to performing a concurrent (b) (4) validation study for the (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 Effected (CBE) supplement no later than December 31, 2026

Final Study Report Submission: December 31, 2026

4. Kedrion commits to submitting a final validation study report to confirm the proposed maximum (b) (4) as a Changes Being Effected (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.*

   Final Study Report Submission: December 31, 2026

5. 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.

   Final Study Report Submission: March 31, 2027

6. 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 Submission – Status Update* by December 31, 2026.

   The method validation and the action limits for (b) (4) in final container will be submitted as a Prior Approval Supplement (PAS) Postmarketing Commitment by December 31, 2027

   Final Study Report by December 31, 2027.

7. 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 30 June 2027.

   Kedrion commits to reporting all stability failures within 45 days of the occurrence as a *Post-Marketing Commitment Submission - Status Update*.

   Final Study Report Submission: June 30, 2027

8. Kedrion commits to providing the (b) (4)

(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).

Final Study Report Submission (qualification summary report (b) (4)-1427-R): December 31, 2025

Final Study Report Submission (stability study report STS-186-R): July 31, 2028

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)

(b) (4)

Final Study Report Submission: February 28, 2027

10. Kedrion commits to evaluate (b) (4) . Kedrion proposes to submit data on (b) (4) and the relevant assessment as a Post-Marketing Commitment by December 31, 2026.

    Final study report submission: December 31, 2026