**Department of Health and Human Services**

**Public Health Service**

**Food and Drug Administration**

**Center for Biologics Evaluation and Research**

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| **To**: | BLA 125105/2184 |
| **From:** | Evi Struble, Ph.D., Research Pharmacology, PDB I, DPD, OPPT, OTP |
| **Through:** | Ewa Marszal, PhD, Branch Chief, PDB I, DPD, OPPT, OTP |
| **Applicant:** | Takeda Pharmaceuticals USA, Inc. |
| **Product:** | GAMMAGARD LIQUID LOW IgA, Immune Globulin Infusion (Human) 10%, IgA less than or equal to 2 micrograms per mL, for intravenous or subcutaneous use |
| **Indication:** | Primary Humoral Immunodeficiency, PI |
| **Subject:** | Nonclinical Pharmacology and Toxicology Review |

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# Introduction

This application is an efficacy supplement to BLA 125105, Gammagard Liquid®, aiming to receive approval for Gammagard Liquid Low IgA® preparation with a label that specifies the product contains IgA less than or equal to 2 µg/mL.

Gammagard Liquid Low IgA, also referred to as TAK-880 in the submission and this review, is a 10% polyclonal human immune globulin G (IgG) preparation, made from pooled human plasma and manufactured by the same process as Gammagard Liquid. Gammagard Liquid received marketing authorization in 2005 and is currently indicated for primary humoral deficiency (PI), multifocal motor neuropathy and chronic inflammatory demyelinating polyneuropathy. To manufacture Gammagard Liquid low IgA, the manufacturing process for the approved product is altered to incorporate (b) (4) changes in running conditions of the anion exchange chromatography step. Specifically, (b) (4)

changes are intended to enhance IgA binding to the column, thus result in reduced concentration in the final product.

Although no explicit claims are made in the label of Gammagard Liquid low IgA about patient population intended to take this product, it is stated in section 5 of the label, Warnings and Precautions, 5.1. Hypersensitivity, that preparations with depleted IgA were shown to be better tolerated by subjects with IgA hypersensitivity.

The final formulation of Gammagard Liquid low IgA is the same as the approved product.

## Pharmacology and Toxicology

Two GLP and three non-GLP nonclinical studies were performed with TAK-880 with Gammagard Liquid as a comparator. A complete review of these studies was performed as part of BLS 125105/1998 review process which received a complete response letter on 05/24/2023. A summary and conclusions are presented here.

### Main Findings

TAK-880 and Gammagard Liquid were comparable in safety pharmacology studies. No clear signal of anaphylactoid reactions were seen when a dose up to 1000 mg/kg of TAK-880 was administered IV in spontaneously hypertensive rats or guinea pigs.

TAK-880 and Gammagard Liquid exhibited no statistically significant differences in their ability to stimulate immune cells and induce hypersensitivity reactions in healthy human whole blood.

### Conclusions

Gammagard Liquid Low IgA and Gammagard Liquid have a comparable safety profile in the preclinical assessments performed. There are no nonclinical pharmacology and toxicology issues that would prevent approval of Gammagard Liquid Low IgA for the PI indication.

The language in the package insert is acceptable from this discipline's perspective.