Summary Basis for Regulatory Action

From:	Chana Fuchs, Application Technical Lead
Through:	Jennifer Swisher, Review Chief, on behalf of Gibbes Johnson, Director, Division of Biologics Review and Research IV, Office of Biotechnology Products, OPQ, CDER
Application number:	BLA 761313
Applicant Name:	Halozyme Therapeutics, Inc.
Submission Date:	September 20, 2022
Proprietary Name:	*No Proprietary Name requested*
Established/Proper Name:	Hyaluronidase human recombinant for further manufacturing use
Intended Use:	Intermediate product for further use by argenx BV under BLA 761304 for manufacturing of the final product Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) under a shared manufacturing agreement (SMA).
Recommended Action:	APPROVAL
Name of Signatory Authority:	Emily Freilich, MD Director (Acting), Division of Neurology 1 Office of Neuroscience, OND, Center for Drug Evaluation and Research

1. Introduction

Hyaluronidase human recombinant for further manufacturing use is an endoglycosidase. The mechanism of action of this protein is through depolymerization of hyaluronan (hyaluronic acid) in the extracellular matrix under physiological condition, thereby increasing fluid movement in that space. When combined or co-formulated with certain injectable drugs, it facilitates the absorption and dispersion of the drug by temporarily decreasing the viscosity of the tissue and increasing mobility of the injected material through the connective tissue in the subcutaneous space.

This BLA for further manufacturing use (BLA-FFM) is submitted under a shared manufacturing agreement with final marketing BLA # 761304 by argenx BV for VYVGART Hytrulo (Efgartigimod alfa and hyaluronidase–qvfc) to enable subcutaneous administration of a high concentration of efgartigimod alpha. Hyaluronidase human recombinant for further manufacturing use under this BLA-FFM is not intended to be used directly in patients. It is intended to be an intermediate product to be sold to argenx BV and is referenced by final product BLA 761304. The intermediate product

under this BLA-FFM will be supplied to argenx BV under a shared manufacturing agreement. The full CMC assessment is documented in separate technical assessment documents.

2. Background

Hyaluronidase human recombinant manufactured by Halozyme Therapeutics, Inc. is marketed as an intermediate in conjunction with other products under product specific BLAs, as well as under Halozyme Therapeutics own BLA for Hylenex recombinant intended to be co-administered as adjuvant with other drugs. The hyaluronidase human recombinant intermediate product described in this BLA-FFM is intended to be sold to another firm under a shared manufacturing agreement to be combined with another biologic product. The approved manufacturing of the hyaluronidase human recombinant described in this BLA-FFM is not necessarily the same as in other BLAs, in that it can occur at different manufacturing sites or by different processes and controls.

3. Chemistry, Manufacturing, and Controls (CMC)

a. Product Summary

Hyaluronidase human recombinant for further manufacturing use is a glycosylated single-chain protein containing up to 447 amino acids with C-terminal variations due to the absence of up to four amino acids. There are six N-linked and one O-linked glycosylation sites, and the major N-glycan species are fucosylated bi-, tri-, and tetra-antennary complex glycans with 0-2 terminal sialic acids N-Acetylneuraminic acid (NeuAc), as well as afucosylated high mannose glycans. This product is produced from a recombinant (b) (4) cell line.

Description of Manufacturing Process

The manufacturing processes and overall control strategies for Hyaluronidase human recombinant for further manufacturing use as described in the license application are appropriately established to ensure consistency and quality of the final product.

In-process controls

The manufacturing process includes specified process controls, including those identified as critical process controls (CPPs), in-process tests (IPTs), and in-process controls (IPCs). These were assessed and found appropriate for the proposed

process. Microbial quality is controlled [redacted] (b) (4) Bioburden and endotoxin samples are monitored at each critical step of the manufacturing process and at release of the intermediate product.

Batch Manufacturing Record (BMR)

Executed batch production records for intermediate product batch [redacted] (b) (4), manufactured at the Avid Myford facility, were provided and reviewed. The batch records include the detailed manufacturing procedures, in-process testing, QC testing results and environmental monitoring records. Review of the BMRs identify that the lots were manufactured in accordance with the validated manufacturing procedures and methods described in the BLA.

Process Validation

A process validation campaign was conducted to support routine manufacturing of the bulk enzyme intermediate at the [redacted] (b) (4) scale. A description of the three consecutive process validation batches were included in the BLA and process data are supportive of the manufacturing process and controls defined in the BLA.

Specifications

Release specifications for Hyaluronidase human recombinant for further manufacturing include testing for appearance, pH, protein concentration, potency, purity by RP-HPLC and SE-HPLC, host cell protein and host cell DNA, bioburden, endotoxin, and identity by tryptic peptide map, IEF, N-linked oligosaccharide profile, and activity assay. Testing for Mycoplasma and in vitro virus is conducted at the [redacted] (b) (4) The acceptance criteria at release and stability are appropriate to ensure product purity and potency at release and for the product shelf life.

Analytical methods

The Applicant provided descriptions and the validation reports for all methods used for lot release and stability testing. The analytical procedures were appropriate for the intended purpose. The assay validations were performed based on predefined acceptance criteria, and results met all the acceptance criteria. The assays have been validated for their intended use.

Reference Standards

(b) (4)

. The referenced standards and protocols were assessed as acceptable for intended use.

Container/ Closure

The primary container closure system for the intermediate product consists of

(b) (4)

Stability

The stability of rHuPH20 intermediate product (10mg/mL Hyaluronidase human recombinant (b) (4) has been evaluated at long-term storage conditions of at -20 ±5°C, and under accelerated stability conditions of 3 months at 5°C and 6 months at 25°C, as well as under stressed (freeze/thaw and photostability) conditions.

Data support the requested expiration dating of (b) (4) months from date of manufacture and is based on (b) (4) months real time stability data from 3 PPQ lots and data from supportive lots manufactured using a comparable process. The date of manufacture for the intermediate product is defined as the date of final filtration and fill operations.

Stability data show that almost all quality attributes were stable without a significant trend of change over (b) (4) months other than for (b) (4)

This resulted in tightening of the release specification to account for this change over time. Notably, the enzyme activity remained stable under all conditions studied.

A stability protocol for the purpose of extending the expiration dating period up to (b) (4) months under 21 CFR 610.12 was included in the BLA.

b. Lot Release

This intermediate product for further manufacturing use is not subject to lot release requirements per 21 cfr 610.2 (b)

c. Facilities Review/Inspection

Facility information and data were provided in the BLA and reviewed by the Office of Pharmaceutical Manufacturing Assessment (OPMA) and found to be acceptable. The decision to waive an inspection was assessed by OPMA and OBP reviewers. Inspections for the manufacturing and testing facilities were waived based on previous pre-license inspections of the same manufacturing processes at the same manufacturing and testing sites for this product, as well as based on an acceptable compliance status of the facilities used for this product.

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Avid Bioservices Inc. 14191 Myford Road, Tustin, CA, United States of America, 92780	3003624288	rHuPH20 bulk enzyme manufacturing, release and stability testing CBI	Approve - Based on Waiver granted by OPMA/OBP
Avid Bioservices Inc. 14282 Franklin Ave., Tustin, CA, United States of America, 92780	3003624288	Release and stability testing for Appearance and Description, pH, Peptide Map, IEF, Protein concentration, RP-HPLC, SE-HPLC, (b) (4) Host Cell Protein, Bioburden, and Endotoxin LCP LMN	Approve - Based on Previous History
(b) (4)			No Evaluation Necessary
			No Evaluation Necessary
			No Evaluation Necessary
			Approve - Based on Previous History

(b) (4)	Approve - Based on Previous History
	Approve - Based on Previous History

d. Environmental assessment
The BLA includes a request for Categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). No extraordinary circumstances exist that would require and environmental assessment; this request is acceptable.

4. Nonclinical Pharmacology/Toxicology
Nonclinical pharmacology and toxicology data were assessed as part of the final product BLA .

5. Clinical Pharmacology
Clinical pharmacology data were assessed as part of the final product BLA review.

6. Clinical
Clinical data were assessed as part of the final product BLA assessment.

7. Safety
Safety information was assessed as part of the final product BLA assessment.

8. Labeling
Labeling of a BLA-FFM is intended to be for manufacturers, and not for health care providers so the format provided below is appropriate for this intermediate product for further manufacturing.

As described in the FDA Guidance titled "Cooperative Manufacturing Arrangements for Licensed Biologics", November 2008, the phrase, "for further manufacturing use" is to be included as part of the proper name when a licensed intermediate product will be approved for further manufacturing use. If included as part of the proper name, the phrase "for further manufacturing use" must appear on the label affixed to each

package containing the product (21 CFR 610.61), as well as the container label, if capable of bearing a full label (21 CFR 610.60).

The following label will be used on each container of the intermediate product for further manufacturing:

Because the primary containers are not transported in a secondary packaging component, a carton label is not required.

9. **Advisory Committee Meeting**
   Not applicable for this submission.

10. **Other Relevant Regulatory Issues**
    None

11. **Recommendation for or agreed upon Post-Marketing Activities**
    None

END OF DOCUMENT

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHANA FUCHS
06/14/2023 08:59:00 PM

JENNIFER F SWISHER
06/15/2023 07:58:08 AM