



FOOD AND DRUG ADMINISTRATION ADMINISTRATION
Center For Biologics Evaluation and Research

MEMORANDUM

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Subject: Original BLA 125495/0.0 for recombinant human C1
Esterase Inhibitor (rhC1INH) [Ruconest]; CMC
review memo of Module 3, Section 3.2.P: Drug
Product, and Chapter 2.3.A: Adventitious Agents
Safety Evaluation

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To the file: STN 125495/0

Action recommended:

Based on my review of the data for Drug Product quality,
this part of the Original BLA 125495/0 is approvable.

General information:

Submission date: 4-16-2013

CBER receipt date: 4-16-2013 (DATS Log #: 557932)

Type of submission: Original BLA

Sponsor: Pharming Group NV. (Pharming), the Netherland

USA Agent/Partner: Santarus

Product: C1 Esterase Inhibitor (Recombinant), rhC1INH

Proprietary name: Ruconest

Non-proprietary International name: *conestat alfa*

Indications: Treatment of acute attacks of hereditary
ngioedema (HAE) in adults and adolescent patients

Administration route: Intravenous (IV)

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BACKGROUND

The Pharming's product, Ruconest is a preparation of rhC1INH produced in the milk of transgenic rabbits. This product is intended for the treatment of acute attacks of hereditary angioedema (HAE) in patients with C1INH deficiency (low level or dysfunctional C1INH in plasma). HAE is a rare autosomal dominant disease with an estimated frequency of 1:50000. The release of bradykinin triggered by low content of functional C1INH results in increased vascular permeability and edema in subcutaneous or submucosal tissues at various body sites (usually face, abdomen, extremities, oropharynx or larynx). HAE acute attacks cause pain and disability, and are potentially life-threatening when edema strikes upper airways.

Human C1INH is a multifunctional plasma glycoprotein. By sequence homology and mechanism of protease inhibition it belongs to the superfamily of serine proteinase inhibitors (serpins). C1INH inhibits several proteases of the major plasmatic amplification cascades, being the only regulator of the Complement cascade and playing a key role in the regulation of the Contact (kallikrein-kinin) pathway, thus keeping bradykinin level under control. It participates in the regulation of the Coagulation and Fibrinolytic cascades and possesses some other biological activities.

C1INH replacement (augmentation) therapy in C1INH-deficient patients became logical option for HAE treatment to increase level of functionally active C1INH in plasma and thus, restore control over the Contact system activation. In Europe, C1INH concentrates derived from plasma have been used for over 30 years. In the US, no HAE targeted therapy was available until 2008, when Cinryze (ViroPharma) was approved, followed by approval of Berinert (CSL Behring)¹.

As an alternative and in addition to plasma-derived C1INH products, in 2010 the recombinant analog of C1INH (rhC1INH) was approved by the European Medicine Agency (EMA). On 4/16/2013, Pharming submitted the BLA for rhC1INH (Ruconest) seeking FDA marketing authorization in the US.

This memo is a CMC review of the DP quality data provided in the BLA Module 3 (Quality), Section 3.2.P: Drug Product, and Chapter 2.3.A Adventitious Agents Safety Evaluation.

DESCRIPTION AND COMPOSITION OF DRUG PRODUCT

¹Karnaukhova, E. C1-esterase inhibitor: Biological activities and therapeutic applications. *J. Hematol. Thromb. Dis.* 1(3): 1-7, 2013

Finished DP rhC1INH is a sterile non-pyrogenic lyophilized powder, white to off-white, preservative-free, sealed in a single use (b)(4) colorless glass vial. Prior to use, it must be reconstituted with sterile Water for Injection (WFI) to a colorless transparent solution (sterile WFI is not supplied with the DP).

The DP is manufactured from the bulk Drug Substance (DS) by sterile filtration and aseptic filling of the formulated bulk DS into glass vials followed by lyophilization.

COMPOSITION AND RECONSTITUTION

The final composition of the formulated DS is adjusted to the target concentration -----
 ----- (b)(4) -----
 -----, the final reconstituted DP contains -(b)(4)- of rhC1INH with its potency of 150 U/mL (Table below):

Table 1: Composition of Drug Product

Ingredient	Quantity per vial*	Quantity per mL after reconstitution	Quality	Function
rhC1INH	2100 U	150 U/mL	-(b)(4)-	Active substance
Sucrose	937 mg	67 mg/mL	-(b)(4)-	---(b)(4)---
Sodium citrate ¹	83.3 mg	6.0 mg/mL	-(b)(4)-	---(b)(4)---
Citric Acid ²	1.0 mg	72 µg/mL	-(b)(4)-	----(b)(4)---

*Based on the extractable volume of 14.0 mL

¹ Sodium citrate dihydrate

² Citric acid monohydrate

After reconstitution with 14 mL of WFI, each vial must contain 2100 U of active DP (-(b)(4)- of rhC1INH) with potency approximately 150 U/mL. The reconstituted solution must be free from visible particles and have pH (~6.8) and --(b)(4)-- (Table above) compatible with IV administration. The impact of shaking during reconstitution has been evaluated with regards to the following key parameters:

Table 2: Results of DP reconstitution at t=0 hours (25°C)

Test	No shaking	Vigorous shaking
Clarity	----- (b)(4) -----	----- (b)(4) -----
rhC1INH activity	---- (b)(4) ----	150 U/mL
---- (b)(4) ----	(b)(4)	(b)(4) ¹
----- (b)(4) -----	(b)(4)	(b)(4)
----- (b)(4) -----	(b)(4)	(b)(4)
---- (b)(4) ----	(b)(4)	(b)(4)

----- (b) (4) -----

RELEASE SPECIFICATIONS

Per release, DP must meet the predetermined criteria of the proposed specification before and after reconstitution:

Table 3: Release Specification for rhC1INH DP

Assay	Method	Specification
Before		
Appearance and description		
Physical state	Visual inspection	Cake
Color	Visual inspection	White to off white
General physicochemical properties		
Reconstitution time (in water)	Time determination	(b)(4)
Water content	--(b)(4)--	(b)(4)
After reconstitution		
Appearance and description		
Color	---- (b)(4) ----	Colorless
Clarity	---- (b)(4) ----	----- (b)(4) -----
Visible particles	---- (b)(4) ----	Essentially free from visible particles
----- (b)(4) -----	---- (b)(4) ----	----- (b)(4) ----- ----- (b)(4) -----
Identity		
----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) ----- -----

Assay	Method	Specification
----- (b)(4) -----	----- (b)(4) -----	<ul style="list-style-type: none"> • ----- (b)(4) ----- ----- (b)(4) ----- ----- • ----- ----- (b)(4) ----- ----- -----
Potency		
rhC11NH activity	----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
Quantity		
Total Protein	(b)(4)	----- (b)(4) -----
Purity		
Purity	(b)(4)	(b)(4)
Product related Impurities		
----- (b)(4) -----	(b)(4)	(b)(4)
----- (b)(4) -----	(b)(4)	(b)(4)
----- (b)(4) -----	(b)(4)	(b)(4)
----- (b)(4) -----	(b)(4)	----- (b)(4) -----
General physicochemical properties		
pH	----- (b)(4) -----	----- (b)(4) -----
----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) -----
Contaminants		
Endotoxins	----- (b)(4) -----	----- (b)(4) -----
Sterility	----- (b)(4) -----	Sterile

Justification of the DP specifications was made on the bases of the data analysis from (b) (4) pilot-scale and (b) (4) full-scale batches (part of which were used in non-clinical and clinical studies), results of stability studies, analytical procedures used for quality control testing, and drug substance specifications.

DP MANUFACTURING FACILITIES

DP Manufacturing (including release and stability testing, labeling, packaging and storage) is being performed by several institutions at the facilities listed below:

Organization/Facility	Responsibility
----- (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) ----- -

¹Facility Establishment Identifier

Reviewer's comment: FDA pre-licensure inspection of the manufacturing facilities in ----- (b) (4) -----

----- scheduled for October 26, 2013
through November 6, 2013 has been postponed.

MANUFACTURING PROCESS AND CONTROLS

Manufacturing of DP starts with formulated bulk DS and results in a sterile lyophilized powder of the finished DP. To assure a consistent and robust DP manufacturing process, several in-process control parameters (shown in the table below) have been validated during the process development:

Table 4: In-process controls and acceptance criteria

(b) (4)

The DP manufacturing process includes the following four major steps:

- (1) ----- (b) (4) -----
- (2) ----- (b) (4) -----
- (3) Filling of vials, and
- (4) Lyophilization.

Reviewer's comment: Please refer to the review memo of the DMPQ's reviewer (Dr. Nancy Waites) for more detailed description of the manufacturing process, process performance qualification and process validation.

Potentially critical steps and control parameters in the DP manufacturing process are summarized in tabular form below:

Table 5: Potentially critical manufacturing steps

(b)(4)

Justification of the in-process control acceptance criteria is provided as follows:

Table 6: Justification of in-process Controls

(b) (4)

Endotoxins (----(b) (4)-----)

Sterility (qualitative)

----(b) (4)---- methods:

Physical state (cake; qualitative)

Color (cake; qualitative)

Reconstitution time (quantitative)

Water content (quantitative)

----- (b) (4) -----

rhClINH activity (quantitative)

----- (b) (4) -----

Purity (quantitative)

----- (b) (4) -----

----- (b) (4) -----

----- (b) (4) -----

Reviewer's comments:

- Review of the validation data for several analytical methods has been performed by the DBSQ/OCBQ reviewers (see review memos by Lokesh Bhattacharyya and Alfred Del Grosso); that includes the following analytical methods:

Potency by rhClINH Activity Assay

Purity ----- (b) (4) -----

---- (b) (4) ----

----- (b) (4) -----

Water content by ---- (b) (4) ----

----- (b) (4) ----

----- (b) (4) ----

Assay for Host-(b) (4) Impurities of rh-C1NH by (b) (4)

- All other analytical methods and their validation protocols in the Module 3. Quality (Chapter 3.2.S.3. Characterization) were reviewed by Dr. Todd Mollan who found them to be adequately validated.
- Module 5 (Clinical Study Reports) includes Chapter 5.3.1. Reports of Biopharmaceutic Studies. It provides 20 Reports of Bioanalytical and Analytical Methods for Human Studies. All these analytical procedures and the validation protocols were reviewed by Dr. Wayne Hicks.
- Qualification of the tests for sterility and bacterial

endotoxins was performed by DBSQC/OCBQ reviewer (see Dr. Hyesuk Kong's review memo).

REFERENCE STANDARDS

----- (b) (4) -----

----- .

----- (b) (4) -----

----- .

----- (b) (4) -----

----- .

STABILITY STUDIES

To support DP shelf-life and storage conditions, stability studies were conducted at $5 \pm 3^{\circ}\text{C}$ to 25 (b) (4) $^{\circ}\text{C}$ / -(b) (4)- and completed through (b) (4) with (b) (4) full-scale validation batches ----- (b) (4) ----- . Included are ongoing stability studies for full-scale batch (b) (4) (current data available through 36 months), and full-scale

batches -----(b)(4)----- (through 24 months). The same container closure system was used in the stability studies.

STABILITY STUDY OF (b)(4) FULL-SCALE VALIDATION BATCHES

The size (number of vials), potency after reconstitution and storage conditions of the (b)(4) validation batches -----(b)(4)----- are summarized in the tables below.

Table 7: DP information for batches -----(b)(4)-----

(b)(4)

Table 8: Storage conditions, time points and testing regiment performed for batches -----(b)(4)-----

Storage Conditions	Time points (months)									
	0	3	6	9	12	18	24	36	48	(b)(4)
5 ± 3°C	A	B	B	B	B	B	B	B	B	C
25 (b)(4)°C / (b)(4)	A	B	B	B	B	B	B	B	B	C

A = testing: appearance (cake); color (cake); water; reconstitution time; purity (b)(4); rhClINH activity; pH; visible particles; color (reconstituted); clarity; -----(b)(4)-----; sterility
 B = testing as presented in A, except for sterility
 C = testing as presented in A with addition of -----(b)(4)-----

All test results of this study met the requirements of the stability specifications and the proposed commercial

specifications, supporting the DP storage through -(b) (4)--
at $5 \pm 3^{\circ}\text{C}$ to 25 (b) (4) $^{\circ}\text{C}$ / -(b) (4)-.

STABILITY STUDY OF (b) (4) FULL-SCALE DP PRODUCTION BATCHES

Stability study of full-scale validation batch (b)(4)

In addition to the --(b) (4)-- full-scale batches -----
 -----(b) (4)----- full-scale batch -(b) (4)-
 manufactured at -(b) (4)-, was placed on stability for
 validation purposes because of the following reasons: (a)
 the size of this batch which is at the upper validated
 batch size range, (b) the maximum number of DP vials to be
 lyophilized in a single production cycle, and (c) the
 maximum hold times to which this batch was subjected during
 the DP manufacturing procedure.

Batch (b) (4) was manufactured from -----(b) (4)-----
 (see table below) and yielded a total of (b) (4) vials of DP.

Table 9: Drug Product information for batch (b)(4)

(b) (4)

The shelf-life was evaluated at various storage conditions
 over -(b) (4)- with testing performed as indicated below:

Table 10: Storage conditions and testing for (b)(4)

Storage Conditions	Time points (months)										
	0	1	3	6	9	12	18	24	36	48	(b)(4)
5 ± 3°C	A	B	B	B	B	B	B	B	B	B	C
25 (b) (4) °C / (b) (4)	A	B	B	B	B	B	B	B	B	B	C
----- --(b) (4) --	A	B	B	B	B	B	B	A	-	-	-

A = testing: appearance (cake); color (cake); water;
 reconstitution time; purity (b) (4); rhClINH activity; pH;
 visible particles; color (reconstituted); clarity; -----
 -----(b) (4)-----
 -----; sterility
 B = testing as presented in A, except for sterility
 C = testing as in A, plus for -----(b) (4)-----.

All test results at these storage conditions (*vide supra*) met the criteria of the stability specifications and the proposed commercial specifications. According to the study results, finished DP is stable for --(b)(4)-- at $5 \pm 3^\circ\text{C}$ to $25 \text{ }^{(b)(4)}\text{ }^\circ\text{C}$ / -----(b)(4)-----
-----.

Stability study of (b)(4) full-scale production batch (b)(4)

The (b)(4) production batch (b)(4) was placed on stability in addition to the validation batches listed above. Batch (b)(4) was manufactured from -----(b)(4)----- (*vide infra*) and produced a total of (b)(4) vials of finished DP:

Table 11: DP information for batch (b)(4)

(b) (4)

The storage conditions and testing regiments were set as follows:

Table 12: Storage conditions and testing for (b)(4)

Storage Conditions	Time points (months)									
	0	3	6	9	12	18	24	36	48	(b)(4)
$5 \pm 3^\circ\text{C}$	A	B	B	B	B	B	B	B	B	A
$25 \text{ }^{(b)(4)}\text{ }^\circ\text{C}$ / --(b)(4)--	A	B	B	B	B	B	B	B	B	A

A = testing: appearance (cake); color (cake); water; reconstitution time; purity (b)(4); rhClINH activity; visible particles; color (reconstituted); clarity;

----- (b)(4) -----
----- endotoxins; sterility

B = testing as presented in A, except for -----(b)(4)-----
-----, endotoxins and sterility

According to the test results (currently available through 36 months), DP batch (b)(4) is stable for no less than 36 months at $5 \pm 3^{\circ}\text{C}$ to $25_{(b)(4)}^{\circ}\text{C}$ / $-(b)(4)-$. All results at these storage conditions complied with the stability specifications and the proposed commercial specifications, consistent with stability data of earlier tested batches.

Stability study of $-(b)(4)-$ full-scale batches

----- $(b)(4)$ -----

Each of these full-scale batches was manufactured from ----
--- $(b)(4)$ -----, yielding a total of -- $(b)(4)$ -- vials
of finished DP with potency ranging from $(b)(4)$ to 150 U/mL:

Table 13: DP information for batches ----- $(b)(4)$ ----

(b)(4)

The stability studies for DP batches ----- $(b)(4)$ -----
----- at the storage conditions and testing intervals set
as indicated below are on-going. Currently available are
test results through 24 months at the storage conditions 5
 $\pm 3^{\circ}\text{C}$ / -- $(b)(4)$ -- and $25_{(b)(4)}^{\circ}\text{C}$ / $-(b)(4)-$ that support
the DP stability (over current period of time).

This study also includes stability at the $-(b)(4)-$
conditions (----- $(b)(4)$ -----) through 12 months with
no visible trends observed for these conditions so far.

**Table 14: Storage conditions and testing of DP
(b)(4) full-scale batches -----(b)(4)-----**

Storage Conditions	Time points (months)									
	0	3	6	9	12	18	24	36	48	(b)(4)
25 (b)(4)°C --(b)(4)--	A	B	B	B	B	B	B	C	B	A
5 ± 3°C	A	B	B	B	B	B	B	C	B	A
----(b)(4)-----	A	B	B	B	A	N/A	N/A	N/A	N/A	N/A

A = testing: appearance (cake); color (cake); water; reconstitution time; purity (b)(4); pH; rhC1INH activity; visible particles; color (reconstituted); clarity; -----
-----; endotoxins; sterility

B = testing: as presented in A, except for -----(b)(4)----
-----, endotoxins and sterility

C = testing: as presented in A, except sterility testing

All test results complied with the specification criteria.

----- (b) (4) -----

----- (b) (4) -----
-----.

----- (b) (4) -----

(b) (4)

----- (b) (4) -----

----- .

----- (b) (4) -----

----- .

----- (b) (4) -----

----- .

STABILITY OF RECONSTITUTED DRUG PRODUCT

A stability study of the reconstituted DP is included in Chapter 3.2.P.8.3. Several parameters indicative for the rhClINH stability (rhClINH potency, ----- (b) (4) -----) were measured after the reconstitution and up to (b)(4) storage at 5°C -(b)(4)-. A possible impact of shaking (during DP reconstitution) was evaluated by conducting the reconstitution in either of two ways: vigorous shaking, or gentle swirling (with no effect determined).

In summary for the stability studies, Pharming provided stability data for ----- (b) (4) ----- full-scale validation batches, (b)(4) full-scale (b)(4) production batch and (b)(4) full-scale (b)(4) stability batches. The data generated during stability studies support the proposed DP shelf-life of 48 months at $5 \pm 3^\circ\text{C}$ / -(b)(4)- to 25 (b)(4) °C / --(b)(4)--.

After reconstitution, the rhClINH DP is stable for 48 hours being kept within the temperature range from 2°C to 25°C.

To prevent possible oxidation, the DP should be protected from light.

ADVENTITIOUS AGENTS SAFETY EVALUATION

The risk assessment includes evaluation of non-viral and viral adventitious agents.

NON-VIRAL ADVENTITIOUS AGENTS

Safety evaluation with regards to non-viral adventitious agents includes the threat of transmissible spongiform encephalopathies (TSE) through the rabbit milk and through chemicals and materials used in the DS manufacturing. The risk of transmission of prion disease through rabbit milk is considered to be negligible in comparison with that known for other species (cattle, goats, and sheep), and TSE diseases have not been reported for rabbits (wild, domesticated or laboratory) under natural conditions. Additional precautions relate to prevention of any accidental contamination via rabbit food (excluding meat and bone meal) in accordance with European directives. Also, according to the Spongiform Encephalopathy Advisory Committee, milk is currently considered unlikely to present any risk of TSE contamination, and so is the skimmed milk containing rhC1INH.

The possibility of TSE contamination associated with chemicals and materials used in the product manufacturing is also assumed negligible as the chemicals used in purification procedures (----- (b) (4) -----) are not animal-related compounds.

VIRAL ADVENTITIOUS AGENTS

For the rhC1INH production, the risk of viral contamination is mitigated by using the following four complementary steps: (1) Control of animal facilities and animal husbandry, and (2) Animal health monitoring including testing for specific viruses (reviewed by Dr. John Dennis), (3) Screening of the skimmed milk intermediate for adventitious viral contaminants, and (4) Viral clearance by the purification process.

There are two targeted virus inactivation/removal steps in the rhC1INH manufacturing process:

- Virus inactivation by aid of solvent/detergent (S/D) incubation with -----
---- (b) (4) -----
- Virus removal by nanofiltration (NF) -----
----- (b) (4) -----.

The product viral safety is additionally supported by three chromatographic steps during the manufacturing process:

- SP Sepharose big bead (SP BB) chromatography (----- (b) (4) -----);
- Q Sepharose high performance (Q HP) (----- (b) (4) -----), and
- Zinc Chelating Sepharose fast flow (ZN FF) chromatography (---- (b) (4) ----).

To validate the virus reduction capacity of the rhC1INH manufacturing steps the selected model viruses were -----

 ----- (b) (4) -----

----- Validation of the virus reduction capacity of the rhC1INH manufacturing process included (b) (4) virus clearance studies. The table below summarizes the virus log reduction data obtained for each manufacturing step:

Table 16: Viral reduction capacity of the manufacturing

Step	Virus Reduction Factor (Log ₁₀)				
	MLV	REO 3	ORF	FCV	PPV
SP BB chromatography	1.8	2.2	1.5	2.3	1.5
Solvent/detergent incubation	≥ 5.8	NA	3.7	NA	NA
Q HP chromatography	NT	4.8	NT	0.8	2.2
Zn FF chromatography	1.1	3.2	3.3	1.9	0.4
Nanofiltration	≥ 5.5	≥ 6.5	≥ 5.8	≥ 6.9	5.8
Total reduction factor	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)

Reviewer's comment: As evident from the table 16 above, the total reduction factor was calculated as if virus reduction factors of all applicable chromatographic steps are additive, however, they are not. The data summarized in this table have been further discussed with Dr. Mahmood Farshid (DH/OBRR/CBER) who confirmed that whereas the presented study appears acceptable and sufficient, the three chromatographic steps very likely clear viruses with the same or very similar mechanisms, and therefore, they are not considered orthogonal and thus, should not be summed up.

Recommendation for necessary corrections has been included in the CBER information request conveyed to the sponsor on October 23, 2013 as follows:

Please note that cumulative viral log reduction should reflect clearance provided by verifiable orthogonal steps in the manufacturing process. The three chromatographic purification procedures in rhC1INH manufacturing process (Table 2.3.A.2-1) are likely to clear viruses by the same or similar mechanism(s) and the independence of clearance mechanism by these steps could not be experimentally verified. Therefore, the addition of their independently generated viral clearance values will result in overestimation of the viral clearance capacity of the manufacturing process. Please revise your total viral log reduction values to reflect contribution from only a single chromatography step and submit the revised estimate to the Agency for review.

On November 13, 2013 CBER received the sponsor's response. Pharming accepted our recommendations and revised the table for viral reduction capacity. The corrected values of total reduction factors (the revised table is not included in the memo) are: for MLV - ≥ 13.1 , for REO 3 - ≥ 11.3 , for ORF - ≥ 12.8 , for FCV - ≥ 9.2 , and for PPV - 8.0.

Reviewer's comment: The sponsor's response is adequate.

The viral safety margins from downstream processing as summarized for two major viral reductions steps only (see below) provide sufficient evidence of viral clearance by the purification process.

Table 17: Viral reduction steps and factors claimed for the rhC1INH manufacturing process

Step	Virus Reduction Factor (Log_{10})				
	MLV	REO 3	ORF	FCV	PPV
Solvent/detergent incubation	≥ 5.8	NA	3.7	NA	NA
Nanofiltration	≥ 5.5	≥ 6.5	≥ 5.8	≥ 6.9	5.8
Total reduction factor	≥ 11.3	≥ 6.5	≥ 9.5	≥ 6.9	5.8

The DP virus safety margins were determined based upon following three factors taken into account: (a) the amount of rabbit skimmed milk required for the production of one human dose of the product, (b) an estimate of the potential viral load in the milk (as based on the detection limit of the assays used for milk screening), and (c) the log reduction factors determined for the claimed steps of the manufacturing process.

Taking into account veterinary control of the transgenic rabbit husbandry, monitoring of rabbit milk donations and milk pools collected for skimming, purification procedure with two dedicated viral clearance steps, and validated virus reduction capacity by the manufacturing process, the risk mitigation with regards to potential contamination of rhC1INH with viral adventitious agents is adequately addressed.

CONCLUSION

Based on my review of the Drug Product quality data provided in the BLA Module 3. Quality, Section 3.2.P: Drug Product, and Chapter 2.3.A Adventitious Agents Safety Evaluation, these parts of the Original BLA 125495/0 are approvable.