

Memorandum

**Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality**

To: 125495/0 Recombinant C1 Esterase Inhibitor (Human)

Elena Karnaukhova, Chair, OBRR/DH/LPD
Nannette Cagun, RPM, OBRR/DBA/RPMB

Cc: Review Committee Members

Alpita Popat, OCBQ/DCM/APLB, Labeling, Promotional Materials
Dominador Manalo, OBRR/DH/LPD, CMC, Product
Charles Maplethorpe, OBRR/DH/CRB, Clinical
Cheryl Hulme, OCBQ/DMPQ/PRB, Other, Quality Control
Laura Polakowski, OBE/DE/AEB, Epidemiology
Yuqun Luo, OBE/DB/TEB, Biostatistics
Iftexhar Mahmood, OBRR/DH, Clinical Pharmacology
Anthony Hawkins, OCBQ/DIS/BMB, BIMO
Jin Baek, OBRR/DH/LPD, Pharm/Tox
Paul Buehler, OBRR/DH/LPD, Pharm/Tox
Todd Mollan, OBRR/DH/LPD, CMC, Product
John Dennis, OBRR/DVS, Other, Product
Catherine Poole, OCBQ/DBSQC/QAB, Other, Product
Hyesuk Kong, OCBQ/DBSQC/LMIVTS, Other, Product
Lokesh Bhattacharyya, OCBQ/DBSQC/QAB, Other, Product
Felice D'agnillo, OBRR/DH/LBVB, Other, Product
Rabia Ballica, OCBQ/DMPQ, CMC Facility Reviewer

From: Nancy Waites, CMC Facility Reviewer, OCBQ/DMPQ

Through: Carolyn Renshaw, Branch Chief, OCBQ/DMPQ/B1

Subject: Primary Review Memo

Indication: Treatment of acute attacks of hereditary angioedema in adult and adolescent patients

Applicant: Pharming Group NV

Facility Sites: -----(b)(4)----- – Rabbit Facility
----- (b)(4)----- Drug Substance Manufacture
----- (b)(4)----- – Drug Product Manufacture

------(b)(4)----- - Labeling,
packaging and storage

Primary Review Memo Due Date Goal: 04 Dec 2013

Final Action Due Date: 16 Apr 2014

Recommendation: The Clinical Review Group received agreement that this submission will **receive a CR**. This review is currently on-going. At this time there are two issues identified to hold up approval of the application. The final decision regarding this application will be determined in the addendum review after the responses to the information requests have been reviewed.

1. The pre-license inspection was postponed based on a decision of the Product Office and agreed to by DMPQ Division and Office Directors. Approval of the application cannot occur until an inspection is performed.

Summary

On 16 April 2013 the FDA received an original Biologics License Application (BLA) submitted electronically in eCTD. The filing memo was completed on 23 Apr 2013 and concluded the application could be filed per 21 CFR 601.2. I initiated my draft review on 27 Sep 2013 due to the lead DMPQ reviewer leaving the division and completed my memo on 06 Dec 2013.

Information Request Dates:

One information request, dated 17 Oct 2013, was sent to Pharming.

I have an additional information request dated 11 Dec 2013 that still needs to be sent to Pharming. I submitted the questions to my Branch Chief for review.

Telecon Dates:

None.

Noteworthy Aspects

The Applicant originally requested a Priority Review; however, this request was denied so the review timeline will follow the standard review timeline for PDUFA V.

It is very difficult to determine exactly which facility is responsible for manufacture of the drug substance and which company is responsible for the manufacture of the drug product. The -----(b)(4)----- module states that ----(b)(4)---- is responsible for DS and DP manufacturing and the --(b)(4)- module states that --(b)(4)-- is responsible for DS and DP manufacturing. The information for the ----(b)(4)----- (rabbit housing, milking of rabbits, and skimming of the milk) is repeated in both the --(b)(4)- modules and the ----(b)(4)----- modules. The same applies to the ---(b)(4)--- packaging facility.

Organization / Site	Responsibility	FEI Number	DUNS Number	Inspection? Y/N
----- -----(b)(4)----- -----	----- ----- ----- ----- ----- ----- -----(b)(4)----- ----- ----- ----- -----			
----- (b)(4) -----				
----- ----- -----(b)(4)----- ----- -----	----- -----(b)(4)----- -----	(b)(4)	-----(b)(4)---- --	N

^a -----(b)(4)-----

The pre-license inspection for the -----(b)(4)----- had been scheduled for the week of 28 Oct – 06 Nov 2013; however, it was postponed until further notice based on the decision of the Product Office to cancel the inspection. This decision to postpone the inspection was agreed to by DMPQ Division and Office Directors. The pre-license inspection of the -----(b)(4)----- facility was scheduled to be performed by the field starting 17 Oct 2013. Due to the decision to postpone the inspection for the other facilities, the field was instructed to not perform the pre-license inspection of the facility at -----(b)(4)----- that is used for the manufacture of the drug substance.

Drug Substance Testing Facilities

Organization / Site	Responsibility	FEI Number	DUNS Number	Inspection? Y/N
----- (b)(4) -----				
----- ----- -----(b)(4)----- ----- -----	----- ----- -----(b)(4)----- ----- -----	-----(b)(4)-----	-----(b)(4)-----	N

Organization / Site	Responsibility	FEI Number	DUNS Number	Inspection? Y/N
	----- -----			

1 Page Determined to be Not Releasable: (b)(4)

Organization / Site	Responsibility	Facility Establishment Identifier	Data Universal Numbering System Number	Inspection Needed?
----- ----- -----(b)(4)----- ----- -----	packaging and storage	(b)(4)		

The pre-license inspection for the ----(b)(4)---- facility and the ---(b)(4)--- facility had been scheduled for the week of 28 Oct – 06 Nov 2013; however, it was also postponed until further notice. Note: * During the filing meeting the decision was made to inspect the labeling and packaging facility, -----(b)(4)-----; however, this decision was reassessed at a later time and the OCBQ Office Director determined that an inspection of the labeling and packaging facility would not be necessary.

Drug Product Testing Facilities

Organization / Site	Responsibility	Facility Establishment Identifier	Data Universal Numbering System Number	Inspection Needed? Y/N
----- ----- -----(b)(4)----- -----	----- ----- -----(b)(4)----- -----	-----(b)(4)-----	-----(b)(4)-----	Yes
----- ----- -----(b)(4)----- -----	----- ----- -----(b)(4)----- -----	-----(b)(4)-----	-----(b)(4)-----	Yes
----- ----- -----(b)(4)----- -----	----- ----- -----(b)(4)----- -----	-----(b)(4)-----	-----(b)(4)-----	No
----- ----- -----(b)(4)----- ----- ----- ----- ----- ----- -----	-----(b)(4)----- -----	-----(b)(4)-----	-----(b)(4)-----	No

Note: During the filing meeting it was decided that the inspection for -----(b)(4)----- did not have to be performed. I do not have documentation for the reason for this; therefore I will have to look up the inspection history of the facility and either write an inspection waiver memo or an inspection will have to be performed. This will be follow-up during the Addendum Review.

Scope of Review

I have performed a review of this application per CBER SOPP 8401.4: Review Responsibilities for the CMC Section of Biologic License Applications and Supplements. I specifically review the contents for the information that falls under DMPQ responsibility for review.

Items Reviewed

The following sections are included in this BLA. I have provided a summary of information provided in the submission that is under DMPQ purview in this review memorandum. The topics of review follow the sections of the eCTD format.

1. FDA Regional Information (shared review)

- 1.1 Forms
- 1.2 Cover Letters
- 1.4 Reference Section
- 1.6 Meetings
- 1.12 Other Correspondence (request for categorical exclusion)

2. Common Technical Document Summaries (shared review)

- 2.2 Introduction
- 2.3 Quality Overall Summary (shared review)
 - 2.3.S Drug Substance (shared review)
 - 2.3.S recombinant human C1 esterase inhibitor (rhC1NH)-All
 - 2.3.P Drug Product (shared review)
 - 2.3.P recombinant human C1 esterase inhibitor (rhC1NH)-All strengths - All

2.3.A Appendices

2.3.R Regional Information (shared review)

3.0 Quality

3.2.S Drug Substance

- 3.2.S recombinant human C1 esterase inhibitor (rhC1NH)-All
 - 3.2.S.1 General Information
 - 3.2.S.1.3 General Properties (shared review)
 - 3.2.S.2 Manufacture
 - 3.2.S.2.1 Manufacturer(s)
 - 3.2.S.2.2 Description of Manufacturing Process and Process Controls (shared review)
 - 3.2.S.2.3 Control of Materials (shared review)
 - 3.2.S.2.4 Control of Critical Steps and Intermediates (shared review)
 - 3.2.S.2.5 Process Validation and/or Evaluation

- 3.2.S.2.6 Manufacturing Process Development
- 3.2.S.4 Control of Drug Substance
 - 3.2.S.4.1 Specification (shared review)
 - 3.2.S.4.4 Batch Analysis (shared review)
 - 3.2.S.4.5 Justification of Specification (shared review)
- 3.2.S.5 Reference Standards or Materials (shared review)
- 3.2.S.6 Container Closure System
- 3.2.S.7 Stability
 - 3.2.S.7.1 Stability Summary and Conclusion (shared review)

3.2.P Drug Product

- 3.2.P recombinant human C1 esterase inhibitor (rhC1NH)-All strengths - All
 - 3.2.P.1 Description and Composition of the Drug Product (shared review)
 - 3.2.P.2 Pharmaceutical Development (shared review)
 - 3.2.P.3 Manufacture
 - 3.2.P.3.1 Manufacturer(s) (shared review)
 - 3.2.P.3.3 Description of Manufacturing Process and Process Controls (shared review)
 - 3.2.P.3.4 Controls of Critical Steps and Intermediates (shared review)
 - 3.2.P.3.5 Process Validation and / or Evaluation (shared review)
 - 3.2.P.4 Control of Excipient
 - 3.2.P.4 Compendial
 - 3.2.P.4.1 Specification (shared review)
 - 3.2.P.4.4 Justification for Specifications
 - 3.2.P.4 NA
 - 3.2.P.4.5 Excipients of Animal or Human Origin
 - 3.2.P.4.6 Novel Excipients
 - 3.2.P.5 Control of Drug Product
 - 3.2.P.5.1 Specifications (shared review)
 - 3.2.P.5.4 Batch Analysis (shared review)
 - 3.2.P.5.6 Justification of Specifications (shared review)
 - 3.2.P.6 Reference Standards or Materials
 - 3.2.P.7 Container Closure System
 - 3.2.P.8 Stability
 - 3.2.P.8.1 Stability Summary and Conclusion (shared review)

3.2.A Appendices

- 3.2.A.1 Facilities and Equipment
- 3.2.A.1 Pharming Group N.V. recombinant human C1 esterase inhibitor (rhC1NH) – 2100 U lyophilized powder for reconstitution - Rhucin

3.2.R Regional Information (shared review)

Amendments Reviewed

I reviewed Amendment 16, received on 11 Nov 2013. The review of this amendment is in a separate review memo.

DMF Reviewed

None

Topics Deferred to Other Review Divisions

I have deferred review responsibilities to the Product Office or other appropriate office as outlined in SOPP 8401.4.

Review Issues and Resolution

Amendments from the Review

Amendment 16 - Responses to Information Request Dated 23 Oct 2013 received 13 Nov 2013.

There will be one additional amendment once my current information request, dated 11 Dec 2013, is sent to Pharming.

Review Issues

The issues identified as possibly affecting DMPQ's ability to approve the submission are listed below:

1. The pre-license inspection has been postponed until further notice.

Review and Comment

Module 1.0

1. FDA Regional Information (shared review)

1.1 Forms

I reviewed the 356h and it appeared to be completely filled out and acceptable.

1.2 Cover Letters

I reviewed the cover letter and do not have any comments. No notable requests were made in the cover letter.

1.4 Reference Section

Letters of Authorization for DMF --(b)(4)-- for ----(b)(4)---- Glass Vials and DMF --(b)(4)-- for - ----(b)(4)----- Lyophilization Stoppers are included in this section.

1.6 Meetings

I reviewed 1.6.3 Correspondence Regarding Meetings. Pharming Included meeting correspondence from as far back as minutes from 2005. I have reviewed only the correspondence that appeared to be applicable to DMPQ CMC review responsibilities. I performed a high-level review of the following correspondence:

- January 9, 2008 CMC Comments
- November 24, 2009 FDA Comments on CMC Briefing Document for IND 11785
- December 3, 2009 CMC Meeting Minutes

I performed a more thorough review of the minutes for October 26, 2011 since that meeting pertained to Pharming's proposed process to show comparability for the manufacture of the drug substance between ----(b)(4)---- located in -----(b)(4)-----, located in --(b)(4)--.

October 26, 2011

Sponsor Question 1:

1. Does the FDA agree that the proposed comparability testing program is sufficient to demonstrate that the drug substance manufactured at the current site is comparable to the drug substance manufactured at the ----(b)(4)---- site?

FDA Response:

Yes, the proposed comparability testing program is adequate to demonstrate that the rhC1INH bulk Drug Substance manufactured at the ----(b)(4)---- site (----(b)(4)-----) is comparable to that currently conducted at --(b)(4)--. Should the BLA be submitted, a complete validation of all steps of manufacturing processes at both sites is expected to be included.

Comments/Questions from the Division of Manufacturing and Product Quality (DMPQ)

1. Please be aware that a comparison of equipment between the two facilities will have to be performed and included in your assessment of comparability. We note you have performed an evaluation of equipment and filters (materials of manufacture, product contact materials, column width and height, storage solutions, etc) in your Risk Assessment; however, we would also like to see this information included in your submission.

2. From Section 1.7.3, Figure 1, it is noted that a -----(b)(4)----- step was added to the Zinc Chelating Sepharose FF Chromatography step which is then followed by an ----(b)(4)----- step. In your submission, please include the rationale for introducing the ----(b)(4)----- steps for the process at the ----(b)(4)---- facility and the supporting -(b)(4)- validation information.

3. In Section 2.5, it is noted the --(b)(4)-- storage conditions are different between the two facilities. In your submission, please include the rationale for the different conditions and the validation data supporting the cleaning conditions and clean hold times of the --(b)(4)--.

4. Section 6.2.6.3 Change of order of process steps (no. 4 and 31) states that "Due to the new order of steps new intermediates are produced." Please be aware that the ----- --(b)(4)----- will have to be evaluated and this information included. Also the new (b)(4) step will have to be qualified. We note that product quality is addressed in your Risk Assessment, but we would also like to see an evaluation of ----- (b)(4)-----

5. Please be aware that shipping validation needs to be performed for shipping of the ----- (b)(4)----- . Information for the shipping validation should be included in the BLA submission.

November 24, 2009 FDA Comments on CMC Briefing Document for IND 11785

Sponsor Question #8

The CMC establishment description information for manufacture of Recombinant human C1 esterase inhibitor (Rhucin®) to include identification of place of manufacture, floor diagrams, and cross-contamination precautions will be filed in the BLA consistent with CBER/CDER August 1996 Guidance for Industry for the Submission of Chemistry, Manufacture and Control Information for a Therapeutic Recombinant DNA-Derived Product for In-Vivo Use. Consistent with FDA CMC guidance for Recombinant DNA –Derived products, water system validation summaries/routine monitoring program description, lyophilization equipment summary reports and relevant computer system validation summary reports will not be included in the BLA but will be available on site for review during the prior approval inspection (PAI),

Does the Agency concur with content and format of facilities information Pharming proposes to submit in the application?

FDA Response:

We agree that you may submit information as consistent with the aforementioned guidance. Please note that lyophilization validation description and results should be included in the process validation section of the BLA. We also recommend that you consider the guidance - Guidance for Industry M4Q: CTD -- Quality, August 2001, for the type of information to submit in a CTD. In particular, please consider the information to be submitted for Appendix A, 3.2.A.1, "Facilities and Equipment". Please see an excerpt of this guidance below:

A diagram should be provided illustrating the manufacturing flow, including movement of raw materials, personnel, waste, and intermediates in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product. Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product should be included.

A summary description of product-contact equipment and its use (dedicated or multi-use) should be provided. Information on preparation; cleaning, sterilization, and storage of specified equipment and materials should be included, as appropriate.

Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination of areas and equipment where operations for the preparation of ---(b)(4)-- and product manufacturing are performed.

1.12 Other Correspondence (request for categorical exclusion)

Pharming requested a categorical exclusion based on 21 CFR 25.31 (a) and (c). To the applicant's knowledge, no extraordinary circumstances exist to disallow this exclusion.

I reviewed the request for a categorical exclusion and found it to be acceptable. A CE memo was written and it was approved on 23 Sep 2013.

Module 2 and Module 3

Note: Modules 2 and 3 were reviewed together since Module 2 is a summary of the information provided in Module 3.

2. Common Technical Document Summaries (shared review)

2.2 Introduction

This Biologics License Application (BLA) summarizes the chemistry, manufacturing and controls (CMC), nonclinical, and clinical data for Ruconest.

Ruconest contains the active substance recombinant human complement component 1 (C1) esterase inhibitor (rhC1INH; International Nonproprietary Name: conestat alfa) purified from the milk of rabbits expressing the gene encoding for human C1INH. The rabbits are maintained in a closed colony that is controlled and routinely monitored for specific pathogens. The skimmed milk is screened for adventitious contaminants prior to further manufacture, and the manufacturing process has been validated to demonstrate capacity for removal and/or inactivation of viruses. Per Pharming, the -----(b)(4)----- of the recombinant form of C1INH is identical to that of human C1INH.

The proposed indication for Ruconest is treatment for acute attacks of angioedema in patients with hereditary angioedema (HAE).

HAE is a rare, serious, autosomal-dominant genetic disorder with an estimated prevalence of one in 50,000. Clinically, patients with HAE experience recurrent acute attacks of soft tissue swelling that can affect multiple anatomic regions, including the gastrointestinal tract, facial tissues, vocal cords and larynx, oropharynx, urogenital region, and/or the arms and legs. These acute attacks are associated with considerable morbidity, and they often require hospitalization and immediate medical intervention. Laryngeal attacks can be life-threatening due to the risk of asphyxiation.

Patients with HAE have an insufficient plasma concentration of functional C1INH, a serine protease inhibitor (serpin) produced mainly in the liver. In the setting of low functional C1INH, C1 activation causes cleavage of complement component 4 (C4). The diagnosis of HAE in untreated patients is confirmed by the presence of reduced C1INH activity levels and low plasma levels of C4.

In the US, currently available medications for HAE include the plasma-derived (pd) C1INH products Cinryze®, for routine prophylaxis against angioedema attacks, and Berinert®, for treatment of acute angioedema attacks. In addition to the pdC1INH products for HAE, two non-blood-derived drugs recently were approved by FDA for treatment of acute angioedema attacks: ecallantide (Kalbitor®), a kallikrein inhibitor, and icatibant (Firazyr®), a bradykinin receptor antagonist.

Safety and Efficacy Data of rhC1INH for the Treatment of HAE

Reviewer Comment: This section provided a synopsis of the clinical trials that were run and the data obtained from those trials. The section included a reference to the clinical database, summary of clinical efficacy, summary of clinical safety, and the Pharmacovigilance Plan.

I did not review this section.

DRUG SUBSTANCE

2.3 Quality Overall Summary (shared review)

2.3.S and 3.2.S Drug Substance (shared review)

2.3.S and 3.2.S recombinant human C1 esterase inhibitor (rhC1NH)-All

2.3.S.1 and 3.2.S.1 General Information

Reviewer Comment: This section of Module 2 covers nomenclature, structure, and general properties such as molecular mass, isoform pattern, etc. I did not review this section since it falls under the purview of the Product Office.

2.3.S.2 and 3.2.S.2.1:Manufacture – -----(b)(4)-----

Reviewer Comment: Organization of this review memorandum

Within Modules 2 and 3 there is information for both -----(b)(4)----- . I have only included information for ---(b)(4)--- in the Drug Substance section of this review memorandum and only information for ---(b)(4)--- in the Drug Product section of this review memorandum. There were not individual sections in the application for the ----- --(b)(4)----- facility; however, I broke the information out into their own sections for clarity. This organization of the review memo was done based on the assertion by Pharming that the commercial manufacturing process *only* occurs in the facilities listed in the Manufacturing and Testing Facilities section of this review memorandum.

2.3.S.2.1 and 3.2.S.2.1 MANUFACTURERS (Overview)

The Drug Substance manufacturing process consists of the following steps:

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

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

2.3.P and 3.2.P Drug Product -----(b)(4)----- (shared review)

Reviewer Note: It was very difficult to review the information provided in the submission since -----(b)(4)----- had drug product manufacturing information listed in their sections. I have only reviewed the information related to ----(b)(4)---- for the manufacture of the drug product.

2.3.P and 3.2.P recombinant human C1 esterase inhibitor (rhC1INH)-All strengths - All DRUG PRODUCT

2.3.P.1 and 3.2.P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

The recombinant human C1 esterase inhibitor (rhC1INH) Drug Product is a sterile, non-pyrogenic, preservative-free, white to off-white Lyophilized Powder for Reconstitution contained in a single use --(b)(4)--, colorless sealed glass vial. The product must be reconstituted with 14 mL sterile Water for Injection (WFI) before use.

The solvent (sterile WFI) for reconstitution is not supplied with the Drug Product.

The Drug Product is manufactured by sterile filtration and aseptic filling of the formulated bulk Drug Substance into glass vials followed by lyophilization. No other components are added in the manufacturing process of the Drug Product. There are no overages in the formulation of the rhC1INH Drug Product.

The final targeted composition of the formulated Drug Substance is -----(b)(4)----- Therefore, final reconstituted product contains nominally -----(b)(4)----- with an rhC1INH potency of 150 U/ mL. The composition of one vial rhC1INH Drug Product is presented in the table below.

Composition of Drug Product

Name of Ingredients	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 - dihydrate	83.3 mg	6.0 mg/mL	---(b)(4)-----	---(b)(4)-----
Citric Acid - monohydrate	1.0 mg	72 µg/mL	---(b)(4)-----	---(b)(4)-----

* The quantities presented are based on the extractable volume of 14.0 mL

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

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

Therefore, it was demonstrated that the container closure system robustly ensures the integrity of the product for a period of at least --(b)(4)--, which is beyond the proposed shelf life of the Drug Product.

Reviewer Comment: I reviewed Appendix 1: Statement for container closure integrity of the primary packaging materials for rhC1INH Drug Product (up to 3 years) and Appendix 2: TEC-PDV-R-03-054 Final report Container closure integrity study -rhC1INH DP validation batches -----(b)(4)----- and determined there was not enough information contained in the appendices to determine the appropriateness of the CCIT studies. The following was added to the IR dated 23 Oct 2013:

In Module 3.2.P.2.4, Appendix 1: Statement for container closure integrity of the primary packaging materials for rhC1INH Drug Product (up to 3 years) and Appendix 2: TEC-PDV-R-03-054 Final report Container closure integrity study -rhC1INH DP validation batches -----(b)(4)-- where included in the application to demonstrate container closure integrity. There was insufficient information to determine the acceptability of the -----(b)(4)----- testing. Please provide the following information:

For the -----(b)(4)----- Test:

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

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

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

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

For the ---(b)(4)--- test:

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

- Provide the sensitivity of the test
- Confirm the vials used in the testing have been exposed to the same manufacturing conditions such as sterilization, filling, capping
- Please indicate how a positive test is determined. Include a description of the vial inspection such as visual inspection or inspection using a spectrophotometer.

I also note, that the (b)(4) material used in the process validation and then subsequently for the stability tests and expiry dates was produced at -----(b)(4)-----is supposed to be the commercial manufacturing site. Pharming has demonstrated that the material manufactured at -----(b)(4)----- and the material manufactured at -----(b)(4)---- is comparable; however, this may not apply to the material placed on stability and used for expiration dating. The information obtained from testing on material manufactured completely at -----(b)(4)---- may support the final expiry date and determination of compatibility between the container closure system and the final product. It will be up to the Product Office to make that determination.

---(b)(4)--- study was performed in which the impact of reconstitution with WFI without shaking and reconstitution with WFI while shaking the reconstituted Drug Product vigorously at 25 -----
------(b)(4)--- on the reconstituted Drug Product was assessed. This study was part of the study in which the stability of reconstituted rhC1INH Drug Product was examined. A summary of the relevant results can be found in the submission in Table 3.2.P.2.6-1.

The data of this study demonstrated that reconstitution with WFI either with or without shaking of the vials during reconstitution did not have a negative effect on the physicochemical and/or biological properties of reconstituted rhC1INH Drug Product. It is therefore concluded that the compatibility of the reconstituted solution with the glass vial and rubber stopper has been demonstrated for up to --(b)(4)---.

Reviewer Comment: I performed a high-level review of the stability of the reconstituted product and found it to be acceptable. Final decision of acceptability will be the responsibility of the Product Office.

2.3.P.3 and 3.2.P.3 MANUFACTURE

2.3.P.3.1 and 3.2.P.3.1: MANUFACTURERS

The manufacturing process of recombinant human C1 esterase inhibitor (rhC1INH) Drug Product is described in 3.2.P.3.3 of this review memorandum. The organizations involved in the manufacture and testing of the rhC1INH drug product are listed in the Manufacturing and Testing Facilities section in this review memorandum.

Reviewer Comment: The exact same information was supplied in both sections for -----
------(b)(4)-----even though the commercial DP is only manufactured at -----
--(b)(4)---. The -(b)(4)-- section stated it was manufactured at --(b)(4)-- while the ----(b)(4)----
section stated it was manufactured at ----(b)(4)----. I only reviewed the ----(b)(4)----
information.

2.3.P.3.2 and 3.2.P.3.2: BATCH FORMULA

INTRODUCTION

In this module the batch size and batch formula of the Drug Product, powder for solution for injection is included.

The Drug Product is manufactured by sterile filtration and aseptic filling of the formulated bulk Drug Substance into glass vials followed by lyophilization and subsequent packaging. No other components are added in the manufacturing process of the Drug Product.

Manufacturing of the formulated bulk Drug Substance is described in this review memorandum in 3.2.S.2.2 (---(b)(4)---).

BATCH SIZE

The starting material for one batch of Drug Product is a -----
 -----(b)(4)----- . The range of Drug
 Product batch sizes is presented in Table 2.3.P.3-1 below.

**Range of Drug Product batch size depending on the number of -----(b)(4)-----
 -----**

[(b)(4)]

The Drug Product batch size ranges therefore from ---(b)(4)---. The number of vials produced from this range of Drug Product batch sizes varies from approximately (b)(4) up to a maximum of approximately -(b)(4)- vials. The maximum number of vials that can be lyophilized in one single production run is also approximately -(b)(4)- vials.

BATCH FORMULA

The -----(b)(4)----- is used as starting material for manufacturing of the Drug Product. No components are added in the manufacturing process of Drug Product resulting in a batch formula of Drug Product with -----(b)(4)----- as presented in the table below. This table lists the batch formula for minimum and maximum batch size of Drug Product.

Composition of rhC1INH -----(b)(4)----- Drug Product (minimum + maximum batch size of Drug Product)

Name of Ingredients	-(b)(4)- formulated Drug Substance*	-(b)(4)- formulated Drug Substance*
rhC1INH	-----(b)(4)-----	-----(b)(4)-----
Sucrose	-(b)(4)-	-(b)(4)-
Sodium citrate	-(b)(4)-	-(b)(4)-
Citric Acid	-(b)(4)-	-(b)(4)-
------(b)(4)-----	-----(b)(4)-----	-----(b)(4)-----

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

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

Reviewer Comment: Since information on the manufacture of the drug product was provided in -----(b)(4)----- sections it was difficult to determine which facility actually manufactures the drug product and at what volumes. The information for the formulation ingredients was the same for -(b)(4)- facilities, but the volumes differed.

The following was include in the IR dated 23 Oct 2013:

Information for the batch size of drug product was provided in section 3.2.P.3.2 Batch Formula for -----(b)(4)----- . It appears the difference between the (b)(4) facilities was -----(b)(4)----- . Please clarify the location (which facility) where the manufacture of the drug product occurs for the commercial process and at what volume the commercial process occurs.

Information for the formulation of the drug substance was provided in section 3.2.P.3.2 Batch Formula for -----(b)(4)----- . It appears the difference between the (b)(4) facilities was -----(b)(4)----- . Please clarify where the formulation of the drug substance in the commercial manufacturing process occurs and at what volume.

2.3.P.3.3 and 3.2.P.3.3: DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS

DEFINITION AND SCALE OF A PRODUCTION BATCH

Introduction

The manufacturing process of recombinant human C1 inhibitor (rhC1INH) Drug Product starts with -----(b)(4)----- . The manufacture of Drug Substance is described in detail in 3.2.S.2.2 (---(b)(4)---). The Drug Product manufacturing process results in a lyophilized powder for solution for injection and is described in section 2. Subsequently the vials are labeled and packaged resulting in the Final Product as described in section 3.

Reviewer Comment: The following was included in the IR dated 11 Dec 2013:

Please include a more detailed description of the filling process such as is it automated, how many vials are filled, what speed, etc.

There was no information in the application for the visual inspection process. It appears the visual inspection may be an -----(b)(4)--- process. Please provide a summary of that process and include any applicable acceptance criteria such as types of defects and classification of defects that are inspected, acceptance criteria for the primary visual inspection and the AQL inspection.

In-process Controls

The in-process tests and acceptance criteria are presented in the table below.

In-process tests and Acceptance Criteria of IPCs during Manufacture of rhC1INH Drug Product

In-process test	Acceptance criteria	Test method
------------------------	----------------------------	--------------------

One Page Determined to be Not Releasable: (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) -----

Reviewer Comment: The above section is acceptable. The in-process testing and acceptance criteria are acceptable. The process hold times are acceptable. Drug Product Lot ---(b)(4)--- was manufactured using the extremes of the process hold times. The lot passed all release testing and it continues to meet acceptance criteria during stability testing.

The submission does not provide any information on the storage location of the vials post-capping and prior to shipping to the CMO for packaging and labeling. This will need to be reviewed during the inspection.

2.3.P.3.4 and 3.2.P.3.4: CONTROL OF CRITICAL STEPS AND INTERMEDIATES
The steps and intermediates in the production process of Drug Product that were defined as critical as well as the measures taken to control these critical parameters are listed in the table below.

Critical steps in the production of rhC1INH Drug Product

Step	Critical parameter	Control measures
----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) ----- -----
---(b)(4)---	----- (b)(4) ----- --(b)(4)--	----- (b)(4) ----- -----

3 Pages Determined to be Not Releasable: (b)(4)

accompanied by a process monitoring study in which additional aspects of the manufacturing process were assessed (Appendix 2).

In the second part of the process validation, a process validation study was performed in which --
------(b)(4)-----

(Appendix 3). In addition to this validation study the upper and lower limits of operational ranges with respect to the process parameters during lyophilization (------(b)(4)-----) were validated (Appendix 4).

Validation of the -----(b)(4)----- process included a study performed to validate -----
------(b)(4)-----
------(Appendix 5, Appendix 6, Appendix 7 and Appendix 8).

Overview of the Validation Activities Conducted for the rhC1INH Drug Product Manufacturing Process

[(b)(4)]

[

(b)(4)

]

Reviewer Note: I performed a high-level review on the following appendices since the information contained in them mostly falls under the Product Office review responsibilities.

- Appendix 1 VAL-R-03-096 (NL0064250) Drug Product produced using -----
----- (b)(4) -----
- Appendix 2 VAL-R-03-097 (NL0065161)
- Appendix 3 VAL-R-03-109 (NL0070573) Drug Product Produced Using -----
----- (b)(4) -----
- TEC-PDV-R-03-050 Comparability of rhCINH manufactured at pilot scale and full scale

Pharming did not mention any deviations in their summary; however, upon review of the executed protocol for Appendices 1 and 2, I noted that deviations were, in fact, recorded.

It was noted that a ----- (b)(4) ----- occurred. It was concluded at the end of the study that the following adjustments to the --- (b)(4) --- process would be made:

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

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

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

----- (b)(5) ----- Pharming determined that the deviation did not adversely impact the process validation because the steps were still within the total drying time. They did not mention if any studies were performed to demonstrate that this deviation truly did not have an impact on the validation. No information was provided on the reason for the ----- (b)(4) -----

The following was included in the IR dated 11 Dec 2013:

In Appendix 1: VAL-R-03-096 (NL0064250) Drug Product produced using -----
----- (b)(4) ----- and Appendix 2: VAL-R-03-097 (NL0065161) you changed the -----
----- (b)(4) -----
----- (b)(4) -----

----- Please provide additional information to support this statement, including additional data from lots manufactured after the validation lots.

In Appendix 3, during manufacture of batch ----- (b)(4) ----- during processing were applied in order to reflect worst case conditions. The maximum -----
----- (b)(4) -----

The results of the validation studies demonstrated that:

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

Reviewer Comment: I reviewed this appendix and found it to be acceptable. I do not have any questions or comments.

Appendices 5-8

The following appendices were reviewed by Rabia Ballica and the review is located in the EDR. I do not have any additional comments.

- Appendix 5 VAL-R-03-085 (R-05-6F7H4F-GWA) -----
----- (b)(4) -----
- Appendix 6 VAL-R-03-083 (R-05-6F7HBG-GWA) Compatibility study of the
----- (b)(4) -----
- Appendix 7 VAL-R-03-084 (R-05-6F7H8B-GWA) ----- (b)(4) -----
- Appendix 8 VAL-R-03-086 (#014202MI) Extractable substances documentation -
----- (b)(4) -----

2.3.P.3.5.3.1.3 and Section 5 Preparation of vials, stoppers, and caps

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

Reviewer Comment: I am assuming CMO is referring to ----(b)(4)---- and not a different entity not identified in the submission. Information on the validation of the --- (b)(4) --- is contained later on in this review memorandum.

2.3.P.3.5.3.1.4 and Section 6 Filter validation

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

Reviewer Comment: This appendix was reviewed by Rabia Ballica and her review memorandum is located in the EDR.

2.3.P.4 and 3.2.P.4: CONTROL OF EXCIPIENTS

Reviewer Comment: The information in this section falls under the purview of the Product Office. I did not review it.

2.3.P.5 and 3.2P.5: CONTROL OF DRUG PRODUCT
2.3.P.5.1 and 3.2.P.5.1: SPECIFICATION

Recombinant human C1 esterase inhibitor (rhC1INH) Drug Product, a Lyophilized Powder for Reconstitution, is tested for release in accordance with the specifications listed in the table below.

The specifications are based on product characterization and process capability derived from batch analysis and stability monitoring of pilot-scale and full-scale batches used during nonclinical and clinical development and in consideration of the precision and/or limit of detection of analytical methodologies.

Release Specification for rhC1INH Drug Product

Assay	Method	Specification
Before reconstitution		
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)----
After reconstitution		
Appearance and description		
Color	----(b)(4)----	----(b)(4)----
Clarity	----(b)(4)----	----(b)(4)----
Visible particles	----(b)(4)----	Essentially free from visible particles
----(b)(4)----	----(b)(4)----	----(b)(4)----
----(b)(4)----	----(b)(4)----	----(b)(4)----
Identity		
----(b)(4)----	----(b)(4)----	----(b)(4)----- -----
----(b)(4)----	----(b)(4)----	• ----(b)(4)----- ----- ----- • ----(b)(4)----- ----- ----- -----
Potency		
rhC1INH activity	----(b)(4)-----	----(b)(4)-----
----(b)(4)----	----(b)(4)-----	----(b)(4)-----
Quantity		

Assay	Method	Specification
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)-----	----(b)(4)----
Sterility	----(b)(4)-----	Sterile

2.3.P.5.2 and 3.2.P.5.2: ANALYTICAL PROCEDURES (-----)(b)(4)-----)

Reviewer Note: I performed a high level review of this section since the review responsibility is with the Product Office or DBSQC. I do not have any comments.

All analytical methods used for control of Drug Product release are listed in the submission in Table 2.3.P.5.2-1.

Reconstituted rhC11NH Drug Product has the same composition as formulated bulk Drug Substance and therefore the same methods can be used for a number of tests. When the same method is used, reference to the appropriate appendix of 3.2.S.4.2 (-----)(b)(4)-----) is made.

Extensive summaries of Standard Operating Procedures (SOP) for analytical methods can be found in appendices of 3.2.P.5.2 (-----)(b)(4)-----) or 3.2.S.4.2 (-----)(b)(4)----). Per Pharming, the methods have been validated for their intended purpose.

The SOPs for the following test methods were included in the submission.

- Clarity
- Drug Product: General analytical method -----)(b)(4)-----
- Sterility test of soluble solids (freeze-dried products) -----)(b)(4)-----
- Appearance by visual examination
- Reconstitution time of rhC11NH
- Water content determination in rhC11NH using -----)(b)(4)-----
- Visible Particles
- Color of Cake by Visual Examination

2.3.P.5.3 and 3.2.P.5.3: VALIDATION OF ANALYTICAL PROCEDURES (-----)(b)(4)-----)

Reviewer Note: I performed a high level review of this section since the majority of the review responsibility is with the Product Office or DBSQC. I reviewed the moisture content validation. I do not have any comments.

Many tests used for release testing and stability testing of rhC11NH Drug -----
----- (b)(4) -----
----- . Therefore, most of the validation results are presented in 3.2.S.4.3 (----- (b)(4) -----).
The remaining tests on the lyophilized cake are included in 3.2.P.5.3 (----- (b)(4) -----).

Water Content

The assay was originally validated by ----- (b)(4) ----- and transferred to ----- (b)(4) -----
Additional validation was performed at ----- (b)(4) -----
----- are therefore qualified to conduct this assay.

Reviewer Comment: It is unclear which location is considered the primary testing location and which location is considered a backup location. This will have to be determined during the inspection.

I reviewed the following appendices and found them to be acceptable:

- Appendix 1 TEC-ANL-R-03-003: Report of investigation of a -----
----- (b)(4) -----
- Appendix 2 TRF-R-03-027: Report of the method transfer of a ----- (b)(4) -----
method for the determination of water

Appendix 2

This document describes the results of the method transfer for the determination of water in rhC11NH drug product from ----- (b)(4) ----- . The performance of the ----- (b)(4) ----- method is judged by comparison of the results obtained by the participating laboratories and by determination of intermediate precision and reproducibility of the method. Though unknown sample variance may play an important role in these experiments, the method transfer can be considered to be completed successfully.

Appendix 1

This document describes the results of an investigation to use --- (b)(4) --- to extract water in rhC11NH drug product at ---- (b)(4) ----

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

2.3.P.5.4 and 3.2.P.5.4: BATCH ANALYSES

Reviewer Comment: I performed a high level review of this section since material in this section falls under the purview of the Product Office.

Recombinant human C1 esterase inhibitor Drug Product is manufactured according to the manufacturing process described in 3.2.P.3.3 and each batch is controlled by the specification as described in 3.2.P.5.1. Batch analyses have been performed on batches produced according to the full-scale process. The batch analyses are performed by methods for release testing as described in 3.2.P.5.2.

The batch analysis results of -(b)(4)- full-scale batches of rhC1INH Drug Product produced from ------(b)(4)----- are presented in the submission in Table 3.2.P.5.4-2.

The batch analysis results of -(b)(4)- Drug Product batches produced form Drug Substance manufactured at ---(b)(4)--- are presented in the submission in Table 3.2.P.5.4-3.

[(b)(4)]

These batches were used in comparability (3.2.S.2.6), process validation (3.2.P.3.5) and stability studies (3.2.P.8)

Reviewer Comment: This is the first time I have seen where Pharming states that full-scale Drug Substance material manufactured at ----(b)(4)----- was used to manufacture drug product at -----(b)(4)----- are included in the submission in the ---(b)(4)----- section for the -(b)(4)- validation batches manufactured at --(b)(4)--. The BPR for ---(b)(4)--- is included in the application. Batch numbers ----(b)(4)----- do not appear to be discussed anywhere within the application except for this section on Batch Analysis. The executed BPR for DP --(b)(4)-- was not included in this application. It is unclear why Pharming chose to not include this BPR.

In addition to the full-scale batches, the batch analysis results of --(b)(4)-- pilot-scale lyophilized

----(b)(4)---- ending up in the final product is reduced to an acceptable level. Compatibility of the Drug Product with the final container/closure components is addressed in 3.2.P.2.6.

The final Drug Product release specification includes tests for residual moisture (water), endotoxins, particulates (visible and ---(b)(4)---), and sterility.

Compatibility of the Drug Product with -----(b)(4)----- is presented in 3.2.P.3.5. Process controls are implemented throughout manufacture (e.g. ---(b)(4)----) that adequately mitigate entry of potential ----(b)(4)--- into the final Drug Product. Compatibility of the Drug Product with the final container/closure components is addressed in 3.2.P.2.6.

The final Drug Product release specification (3.2.P.5.1) includes tests for residual moisture (water), endotoxin, particulates (visible and ----(b)(4)---), and sterility.

2.3.P.5.6 and 3.2.P.5.6: JUSTIFICATION OF SPECIFICATION

Reviewer Comment: The majority of the tests fall under the purview of the Product Office or DBSQC. I only reviewed water content and found it to be acceptable.

The justification of the proposed acceptance criteria for test parameters used for quality control testing of recombinant human C1 esterase inhibitor (rhC1INH) Drug Product is presented in this section.

The following is taken into account as basis for the justification of the specification:

- Batch analysis data from pilot- and full-scale batches of which a number have been used in nonclinical and clinical testing;
- Effects observed during stability studies. Results of stability studies are presented in 3.2.P.8.3;
- Precision of the analytical procedures used for release testing (see 3.2.S.4.3 or 3.2.P.5.3); The analytical test methods used for quality control testing are described in 3.2.S.4.2 or 3.2.P.5.2;
- Drug Substance specification as presented in 3.2.S.4.1.

I did not review the following test specifications:

- Appearance
- Color
- Reconstitution time (in water)
- Color (after reconstitution)
- Clarity (after reconstitution)
- Visible particles (after reconstitution)
- -----(b)(4)-----
- -----(b)(4)-----
- -----(b)(4)-----
- rhC1INH activity (after reconstitution)

- -----(b)(4)-----
- -----(b)(4)-----
- Purity (after reconstitution)
- -----(b)(4)-----
- -----(b)(4)-----
- -----(b)(4)-----
- -----(b)(4)-----
- -----(b)(4)-----
- Endotoxin (after reconstitution)
- Sterility

Water content

Acceptance criterion

Not more than (b)(4)

Justification of acceptance criterion

The average release result and standard deviation of -----(b)(4)----- is presented in the submission in Table 3.2.P.5.6-3. The batch data are presented in Table 3.2.P.5.6-4. These results justify the proposed acceptance criterion, since the highest value of the statistical range approximates the proposed upper limit of (b)(4) and also take stability data into consideration.

Reviewer Comment: The acceptance criterion set for water content is acceptable.

2.3.P.6 and 3.2.P.6: REFERENCE STANDARDS OR MATERIALS

Reviewer Comment: I did not review this section since it falls under the purview of the Product Office.

MODULE 2.3.P.7 and 3.2.P.7: CONTAINER CLOSURE SYSTEM

The primary container closure system of rhC11NH Drug Product, Lyophilized Powder for Reconstitution, consists of a 25 mL glass vial (-(b)(4)-) as the primary container, a ----- (b)(4)---- rubber stopper and a crimp cap flip-off seal of aluminum and colored plastic. The materials used for the manufacture of the primary container closure system comply with the relevant -----(b)(4)----- for glass containers and elastomeric closures for containers for freeze-dried powders.

Glass Vials 25 mL (---(b)(4)---

The primary container (vials) is supplied by -----(b)(4)-----, and consists of colorless glass (-(b)(4)-) in compliance with -----(b)(4)-----.

The description, drawings, specifications and a certificate of testing for the glass vials are provided in the submission in Appendix 1. The vials are washed and -----(b)(4)----- prior to use in the manufacturing process.

Reviewer Comment: None of the drug products on stability and discussed in this section were manufactured from material made at ----(b)(4)----- . Even though Pharming states in the batch analysis section that Batch numbers -----(b)(4)----- were placed on stability the results are not included in this application. These batches were manufactured from DS made at ----(b)(4)----- . This submission was submitted Oct 2013 and the batches were manufactured in -----(b)(4)-----

Reviewer Comment: On 06 Sep 2013, Pharming provided a stability update in Amendment 10. All lots manufactured from ---(b)(4)--- met specifications. The data covered 12 months.

Stability data of (b)(4) full-scale batches up to ----(b)(4)----full-scale batch up to 36 months and (b)(4) full-scale stability batches up to 24 months are available. Based on the results of these studies, and supported by a statistical evaluation, a shelf life of 48 months is proposed. All assays used for the stability studies have been validated for their intended purpose. Test descriptions can be found in 3.2.P.5.2. Justifications of the specifications are given in 3.2.P.5.6.

Stress studies have been completed, which include -----(b)(4)-----

POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

Storage conditions and time points of the long-term post-approval stability study are indicated in the submission in Table 2.3.P.8-8. The commercial container closure system has been described in 3.2.P.7.

Storage condition and time points of the long-term post-approval stability study (DP batches -----(b)(4)-----)

Condition	Time points (months)									
	0	3	6	9	12	18	24	36	48	(b)(4)
25----- (b)(4)-----	A	B	B	B	B	B	C	C	A	A

A = testing: see Table 2.3.P.8-9

B = testing: as presented in Table 2.3.P.8-9, with the exception of tests for -----(b)(4)-----, endotoxins and sterility

C = testing: as presented in Table 2.3.P.8-9, with the exception of the test for sterility

Analytical test methods and acceptance criteria

The specifications, analytical methods and validation of the methods are described in 3.2.P.5.1, 3.2.P.5.2 (and 3.2.S.4.2), and 3.2.P.5.3 (and 3.2.S.4.3), respectively. The tests and acceptance criteria for stability samples are shown in Table 2.3.P.8-9.

Stability commitment

Pharming commits to the completion of the stability studies for Drug Product batches ----- (b)(4)----- (see 3.2.P.8.1 for the protocols and 3.2.P.8.3 for the data collected to date) up to ----(b)(4)----.

Pharming commits to performing a long-term post-approval stability study for three Drug Product batches -----(b)(4)----- . These batches are derived from Drug Substance produced at ----(b)(4)----, while all above mentioned Drug Product batches are derived from Drug Substance produced at ----(b)(4)----. In addition, at least one production lot will be placed on stability annually after approval according to the protocol as described in Table 2.3.P.8-10.

Storage condition and time points of the annual post-approval stability study for rhC11NH Drug Product

Condition	Time points (months)				
	0	12	24	36	48
25 -----(b)(4)-----	A	B	B	B	C

A = testing: see Table 2.3.P.8-9

B = testing: as presented in Table 2.3.P.8-9, with the exception of tests for -----(b)(4)----, endotoxins and sterility

C = testing: as presented in Table 2.3.P.8-9, with the exception of the test for sterility

CONCLUSIONS

Stability data of (b)(4) full-scale batches up to --(b)(4)-----full-scale batch up to 36 months and (b)(4) full-scale stability batches up to 24 months are available. Based on the data collected, and supported by a statistical analysis (see 3.2.P.8.3), a shelf life of 48 months at 5 ± 3°C to 25 -----(b)(4)---- is proposed. Reconstituted Drug Product is stable for ---(b)(4)--- when stored between 2°C and 25°C.

It is recommended to keep the Drug Product protected from light as it has been shown to be sensitive to light with respect to oxidation.

3.2.A.1: FACILITIES AND EQUIPMENT -----(b)(4)-----

Reviewer Note: This section described drug substance manufacturing and drug product manufacturing at ----(b)(4)----. I have only included information on drug product manufacturing at ----(b)(4)----. It is also difficult to interpret the information because the facilities are often referred to as “the CMO” without a name given so I have to infer which facility they are discussing.

Facility

----(b)(4)----- is responsible for sterile filtration, filling and lyophilization of Drug Product. Details of the Drug Product production process are provided in 3.2.P.3.3. Information on the facility for filling and lyophilization is provided in Appendix 12. The information provided in this appendix concerns: introduction, use of equipment, lay-out of the facility, water, HVAC and air handling, facility maintenance, personnel and material flow, facility sanitization and cleaning procedures. Water is only used for cleaning of materials and equipment as no formulation of API is required in the Drug Product process.

The current non-solids clean rooms have their own HVAC system. Air from outside is filtered by an (b)(4) pre-filter, cooled, dehumidified, heated and humidified and filtered by an (b)(4) filter. In

the ceiling before entering the room the air is filtered by a HEPA filter (---(b)(4)----). The laminar airflow zone (class (b)(4)) has a separate HVAC cabinet with full recirculation.

There is a positive pressure differential of at least -(b)(4)- between adjacent rooms of different classification. A physical and microbiological monitoring program is in place to monitor the status of the clean rooms.

Appendix 12 Facilities and equipment CMO Drug Product Recombinant human C1 inhibitor Powder for injection Facilities and equipment (b)(4) building --(b)(4)--

Introduction

At this site both sterile and non-sterile preparations are manufactured. This document only covers the parts of the facility where the finished product of recombinant human C1 inhibitor Powder for injection is manufactured ((b)(4) building, see Figure 1).

Reviewer Comment: I reviewed Figure 1: Site plan with indication of location of (b)(4) building and do not have any comments.

In the (b)(4) building sterile and non-sterile dosage forms are manufactured for toxicological, clinical and commercial use. Sterile products for both the companies own use and for third parties are manufactured at the -(b)(4)- floor of the (b)(4) building.

Reviewer Comment: Insufficient information is provided on the multi-product facility and the process and procedures in place can prevent cross contamination.

The following question is included in the IR dated 11 Dec 2013:

Based on the description of the filling facility, ---(b)(4)---, it is a multi-product facility. Please provide the following information:

- Additional information about the other types of products that can be filled in the filling rooms on the (b)(4) floor where rhN1INH is filled.
- Please indicate how cross-contamination is mitigated such as thorough cleaning validation, single use materials, area/line clearance, etc.

Facility

The (b)(4) building was constructed in (b)(4). The building consists of (b)(4) levels. Above every production floor and at the inner core of the building there is a technical area. The technical areas have a separate entrance and preventive maintenance and calibration can be done independently from production activities. Offices are located on the same floor as the technical areas. The warehouse and weighing cubicles are located on the --(b)(4)-- floor. The non-solids clean rooms are located on the (b)(4) floor (see Figure 2). The walls, floors and ceilings of clean rooms have a smooth cleanable finish which is impervious to liquids and resistant to sanitizing and cleaning solutions.

Reviewer Comment: I reviewed Figure 2: Floor plan with clean room classification for the (b)(4) floor of the (b)(4) building and found it to be acceptable. The room numbers, activity in each room, and room classification are listed in a table and an accompanying floor plan is color coded for the different area classifications. The grade (b)(4) filling area was surrounded by Grade (b)(4). I do not have any further questions or comments.

Water

Water for injection is produced using a -----(b)(4)----- . It is used for -----
 -----(b)(4)-----

Purified water and water for injection comply with microbiological, chemical and physical requirements in line with pharmacopoeial monographs. The monitoring program for WFI is given below. When limits are exceeded the deviation is handled in a validated system. If the viable count limit is exceeded the organism is to be identified and the test is repeated on a fresh sample.

Monitoring program for water for injection

(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)-----	> 65°C

Reviewer Comment: ------(b)(5)-----
 -----These are important because they come in contact with product contact components such as vials and stoppers.

HVAC and air handling

The (b)(4) building consists of (b)(4) HVAC systems. The current non-solids clean rooms on the (b)(4) floor and have their own HVAC system. Air from outside is filtered by an (b)(4) pre-filter, cooled, dehumidified, heated and humidified and filtered by an (b)(4) filter. In the ceiling before entering the room the air is filtered by a HEPA filter ((b)(4) filter). The laminar airflow zone (class (b)(4)) has a separate HVAC cabinet with full recirculation.

The HVAC system in (b)(4) is zoned. The facility is equipped with a dedicated HVAC system, ID code ---(b)(4)---, which has passed an initial qualification consisting of IQ, OQ and PQ.

In the PQ the following items were checked:

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

For the Grade (b)(4) area, a revalidation is performed each --(b)(4)-- with the following checks:

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

For the Grade ----(b)(4)-- areas a revalidation is performed each (b)(4) with the following checks:

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

There is a positive pressure differential of at least --(b)(4)-- between adjacent rooms of different classification. A physical and microbiological monitoring program is in place to monitor the status of the clean rooms. Physical monitoring is performed in class ----(b)(4)---- rooms in line with GMP requirements. Sample points have been selected for worst-case monitoring. A continuous registration system for particles is in place. Action and alert limits have been set per GMP class.

The microbiological limits have been set in line with (b)(4) GMP guidelines ((b)(4) guide to Good Manufacturing Practice --(b)(4)-) and ---(b)(4)--- (see Table 4). The microbiological limits are re-assessed ---(b)(4)- based on a statistical evaluation of the results obtained and they are adapted when necessary. When limits are exceeded an investigation is started. The impact on the manufacturing batch involved is assessed and the measures to be taken before restart of production are agreed with quality management.

Physical and microbiological monitoring limits applied.

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

Reviewer Comment: No EM results were provided in the submission. -----
-----**(b)(5)**-----

Personnel

Health requirements are in place for personnel engaged in production, including medical examinations. Any health condition that might have an adverse effect on products must be reported to supervisory personnel so that appropriate measures can be taken if necessary.

All employees that work in the non-solids area receive training on the job. The program is set up specific for the employee. For complex equipment like filling equipment, experience needs to be gained before the employee can use it without supervision. For such complex equipment re-training is necessary if the employee does not use it for **-(b)(4)-** years.

Every new employee includes training in working under GMP guidelines. This training includes gowning, behavior in the clean room, performing line clearance and how to handle deviations. The training includes reading of SOPs and attending an internal or external GMP course. Specific attention is given to working in clean rooms under LAF during the media fill training. Compliance with gowning procedures is performed by random microbiological sampling. Compliance with aseptic techniques is monitored by **--(b)(4)--** requalification media fill runs.

Material flow

A flow diagram of the facilities illustrating the flow of materials is provided in Figure 3.

Reviewer Comment: I reviewed Figure 3: Flow diagram of materials in the non-solids area in the **(b)(4)** building and found it to be acceptable. The floor plan depicts the flow of materials and non-finished product with green arrows and the finished product with red arrows. The floor plan must be reviewed with the prior floor plan in order to determine exactly what is occurring. The product goes from areas with less room classifications to areas of higher classification (Not classified – Grade **(b)(4)** – Grade **(b)(4)** – Grade **(b)(4)** – Grade **(b)(4)** and then the reverse).

Facility sanitation and cleaning procedures

Validated cleaning procedures are used. The floor is disinfected using disinfectants after production of a batch. --(b)(4)-, an outside contractor performs an extra cleaning and disinfecting procedure. Control of the efficacy of the disinfection procedure of the Class (b)(4) area is part of the microbiological monitoring program. All equipment in direct contact with the product is dedicated and used ---(b)(4)---. The freeze-dryer does not come into direct contact with the product.

Reviewer Comment: -----(b)(5)-----

Equipment and Materials

Equipment

The equipment used in the production of Drug Product at ----(b)(4)---- is listed in the table below. This table indicates where the equipment is used in the rhC1INH Drug Product process. A short description of the equipment is provided which includes whether the equipment comes into contact with the product. For the Drug Product process there is no contact of product with equipment. The product only comes into contact with single use and disposable materials. During all steps of the process after the -----(b)(4)----- closed systems are used to avoid contamination of the product.

Equipment	Use	Description
----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) ----- ----- -----
----- (b)(4) -----	----- (b)(4) -----	----- (b)(4) ----- ----- ----- -----
----- (b)(4) ----- filling and capping machine	Filling of vials, capping of vials	----- (b)(4) ----- ----- No product contact.
----- (b)(4) -----	Filling of vials	----- (b)(4) ----- ----- ----- No product contact.
-(b)(4)- freeze-dryer	Lyophilization	----- (b)(4) ----- No product contact.
---(b)(4)--- vial washing machine	Cleaning of vials	No product contact.
Scales	----- (b)(4) ----- -----	----- (b)(4) ----- ----- -----

Equipment	Use	Description
Scales	----- (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) ----- -----

Reviewer Comment: The equipment listed below will need to be reviewed during inspection.

The following was included in the IR dated 11 Dec 2013:

The translated batch production record (BPR) for the manufacture of the drug product includes a ----- (b)(4) ----- equipment in the equipment list. This ----- (b)(4) ----- machine is never mentioned in the application. Please comment.

There is no information in the application on the pieces of equipment listed below. Please provide a description of each piece of equipment along with summaries of qualifications performed. This equipment is important and they are considered part of the aseptic fill and lyophilization processes.

- ----- (b)(4) ----- filling and capping machine
- ----- (b)(4) ----- the information provided in the application is ----- (b)(4) -----

- ----- (b)(4) ----- vial washing machine
- ----- (b)(4) -----
- ----- (b)(4) -----
- ----- (b)(4) -----

Materials

The table below lists the materials used in the rhC1INH Drug Product process. An explanation is provided regarding use of materials and a short description of the materials is provided. In addition, it is indicated whether the material comes into contact with the product. For a description of the primary packaging materials see 3.2.P.7.

List of materials

Material	Use	Description
----- (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) ----- -----	--- (b)(4) ---	----- (b)(4) ----- ----- -----

Reviewer Comment: There is no information on the preparation for use of the -----
----- (b)(4) ----- (b)(5) -----

Validation of sterilization ----- (b)(4) ----- processes

--- (b)(4) --- sterilization methods are used for materials used in the rhC11NH Drug Product manufacturing process. -----

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

----- . From the validation studies it is concluded that the sterilization ----- (b)(4) --- processes are validated and that ----- (b)(4) ----- are suitable for their intended use.

Appendix 13 Facilities and equipment: sub report validation sterilization ----- (b)(4) ----- processes

INTRODUCTION

Validation of the sterilization -----(b)(4)--- equipment is summarized in this report. After initial validation the equipment is revalidated ---(b)(4)---. A summary of the results of the latest revalidation performed in 2008 is also included. A maintenance contract is in place with a specialized supplier. Change control is performed in line with GMP requirements.

STERILIZATION -----(b)(4)----- OF CONTAINERS, CLOSURES, EQUIPMENT, AND COMPONENTS

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

VALIDATION OF THE STERILIZATION EQUIPMENT

4 Pages Determined to be Not Releasable: (b)(4)

Reviewer Note: -----(b)(5)-----.

The following was included in the IR dated 11 Dec 2013:

There is insufficient information provided in the application to determine the acceptability of the media simulations. Please provide the following:

- a) A summary of the media simulation. Include a description of the entire process starting when the drug substance is -----(b)(4)-----
- b) While it is never explicitly stated in the submission, I am assuming the filling process is an ----(b)(4)---- process. Please include process parameters such as -----(b)(4)-----
- c) Acceptance criteria for vial ---(b)(4)-- and number of vials allowed to be contaminated, if any.
- d) Please confirm environmental monitoring and personnel monitoring occur during the media simulation, especially during setup of the equipment and after each intervention.
- e) A description of the number and types of interventions performed during the simulation.
- f) Please confirm a batch record is used during the media simulation.
- g) Please indicate the number of vials filled and confirm this is representative of an rhC1INH fill.
- h) Please indicate if growth promotion testing was performed on the media in the vials after they were filled -----(b)(4)-----
- i) Please provide the -----(b)(4)----- required for the vials during a media simulation.
- j) Please provide a description of the freeze drying performed during the media simulation.
- k) -----(b)(4)-----
----- . Please confirm this step is also performed during the media simulation.
- l) Please summarize the qualification of the hold time -----(b)(4)-----
- m) -----(b)(4)-----
----- . Please confirm that all sampling is reproduced during the media simulation.

2.3.A.2: ADVENTITIOUS AGENTS SAFETY EVALUATION

Reviewer Comment: This section falls under the purview of the Product Office. I did not review it.

3.2.R Regional Information - ----(b)(4)-----

The concerned information is provided in the following sections of Module 3.2.R:

Section 3.2.R.1 Comparability Protocol: A Comparability Protocol is designed to demonstrate the comparability of the product produced at the current DSP production scale and site and the product produced at the new DSP production scale and site according to ICH Q5E.

Reviewer Comment: I performed a high-level review of this section and it appears to show comparability between the DS manufactured at ----(b)(4)----- and the DS manufactured at -----(b)(4)----- . The final determination of acceptability belongs with the product office.

Section 3.2.R.2 Executed batch records: Information is provided for released Batch Records of the Drug Substance as well as for the Drug Product batches. If applicable, translations are included when original documents are not in the English language.

Batch records from all of the facilities are included in this section. I reviewed only the records for the drug substance manufactured at ----(b)(4)----. The following drug product batch production records (BPRs) were included in this section:

- BMR Drug Product – batch ---(b)(4)--- – Executed Batch Record
- BMR Drug Product – batch ---(b)(4)--- – English translation EBR
- BMR Drug Product – empty – Dutch

Reviewer Comment: The BPRs are for Batch -(b)(4)--. This drug product was manufactured in -(b)(4)- from drug substance manufactured at ----(b)(4)----. More recent BPRs will need to be reviewed during inspection. In addition the BPRs for drug product manufactured using DS from --(b)(4)-- will need to be reviewed.

The following comments were included in the IR dated 11 Dec 2013. I do not expect a response to these comments.

I have the following comments about the BPRs. These comments are not all inclusive. The BPRs are not sufficiently detailed to allow for consistent manufacturing. For example:

- a) It is unclear if the filling process is automated or manual since there is not a description of the setup of the equipment.
- b) Step NM03 states to “Inspect all vials according to the valid inspection criteria.” No valid inspection criteria are listed and there is no place in the BPR to record the number of vials rejected and the reason they were rejected.
- c) It is unclear if the visual inspection is an automated or manual process since the BPR does not capture the setup of any equipment.
- d) In step NM04, the operator is instructed to “Determine the required number of AQL samples and collect these from the batch -----(b)(4)----- There is no instruction on how to make that determination.
- e) Step NM05 stated “Perform an AQL check” and record the -----(b)(4)----- ----- There is no indication of the types of defects being inspected for during the inspection. There is also no place to record what the defects were and how many vials of the different types of defects were observed.
- f) Numerous times within the BPR the operator is instructed to “Print the batch data from the previous step using HDAS and check the data. Insert as an appendix.” There is no indication what the operator is checking the data for and what is considered acceptable data. No appendices were included in the executed BPR so I am unable to determine if there were any issues encountered during the run.
- g) Step VWF09 states to -----(b)(4)----- ----- There are no instructions on how to perform this step. If the operator is required to use an SOP for the filling set-up, no SOP is referenced. This does not ensure consistent set-up of the filling apparatus.

Section 3.2.R.3 Method Validation Package: Information is listed regarding the validation protocols and reports, and transfer reports, analytical methods, respectively for -----(b)(4)-----, and drug product (DP) (----(b)(4)----).

Reviewer Comment: I did not review this since it falls under the review responsibilities of the Product Office.

Section 3.2.R.4 Information on Components: Information is provided on the organizations involved in the manufacture and testing of the rhC1INH Drug Substance and rhC1INH Drug Product produced at the ----(b)(4)---- site and the -----(b)(4)----- site, respectively.

Reviewer Comment: I did not review this since it falls under the review responsibilities of the Product Office.

2.3.A.1.5 CMO FOR SECONDARY PACKAGING AND STORAGE - ----(b)(4)-----

This section describes the labeling and packaging process of rhC1INH Drug Product vials including in-process controls. The labeling and packaging process consists of a labeling step of the individual vial and packaging of one vial together with a package leaflet in an outer package resulting in Final Product.

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

The packaging facility is designed to support a unidirectional flow of materials. A floor plan of the facilities with flow of product and materials is provided in the submission in Appendix 15.

All packaging lines are physically segregated. -----(b)(4)----- of product is performed in areas which are ventilated through ---(b)(4)- filters with recirculation of air through --(b)(4)-- filters. The temperature in the packaging facility is controlled at --(b)(4)--

Before and after labeling and packaging a line clearance is performed. The process flow for labeling and packaging of rhC1INH Drug Product is described below. After labeling and packaging, the product is stored at 2 to 25°C until distribution.

Appendix 15 Facilities floor plan with flow of product and materials – Packaging Facility

This appendix was a floor plan for the packaging facility.

Reviewer Comment: The physical layout appears to be acceptable; however, there was no description or key to what the different colored arrows signified. There is an airlock and gowning facilities.

Narrative of the packaging process

(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) -----

Reviewer Comment: Information to record during the inspection:

- The description of the process for labeling of the vials is insufficient. I cannot determine if it is an automated or manual process.
- It is unclear where the vial labels are printed or how lot number and expiration date are added to the vial labels or cartons.
- No BPR was submitted for this phase of manufacturing. Review the BPR and confirm it is acceptable.

The following was included in the IR dated 11 Dec 2013:
Please provide a list the equipment used in labeling and packaging of the vials and a summary of their qualifications.

Shipment of Drug Product and Final Product

Shipment of Drug Product vials from -----**(b)(4)**-----, takes place at --**(b)(4)**-- under controlled conditions. During this shipment the temperature is continuously monitored.

Reviewer Comment: -----**(b)(5)**-----