**From:**    Alfred V. Del Grosso, Ph.D., OCBQ/DBSQC Team Leader Analytical
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             Noel Baichoo, Ph.D., OCBQ/DSBQC HFM-681


**Subject:**  DBSQC Test Methods Review Memo for BLA submission, STN#125495,
              Recombinant human C1 esterase inhibitor (rhC1INH), Pharming Group N.V.

**To:**      STN: #125495

**Through:**  Lokesh Bhattacharyya, Ph.D., OCBQ/DBSQC/Chief LACBRP HFM-682

             William M. McCormick, Director OCBQ/DBSQC HFM-680

**Summary of Review:**  This BLA was submitted for Ruconest (recombinant human C1 esterase inhibitor, rhC1INH) by Pharming Group NV (STN#125495).  This memo addresses reviews of the analytical methods for drug substance and drug product.

At the time of this review, the analytical methods and supporting information as listed have been evaluated.  It is our recommendation that the following additional information and commitments be obtained from Pharming Group NV.

   a) **Water Content by --------(b)(4)-----------**
As of 12/09/2013 a Validation Report for this method has not been received.  In their IR response of 10/15/13 Pharming Group had indicated that this would be submitted by 11/22/13.  It is requested that the sponsor submit the report to allow the evaluation of the adequacy of this procedure.

   b) **-------------------------------------(b)(4)-----------------------------------------**
The proposed limits test for the impurities -------------(b)(4)--------------------- **is** acceptable on an interim basis for the approval of this product.  It is our recommendation that Pharming be asked to commit to the submission of a quantitative assay for the determination of these impurities.

c) **Determination of the concentration of ----------(b)(4)----------- in rhC1INH using (b)(4)**

In the response of 10/15/13 to CBER's information request made on 9/17/13, a commitment was made to an expanded robustness study to evaluate changes in --------------------------------------------------------------------(b)(4)----------------------------------------------------------------------------------. It is our recommendation that Pharming be asked to commit to a date for submission of the expanded robustness study.

**Review Summaries**

1) **Potency by rhC1INH Activity Assay, ----(b)(4)----**
   **Reviewer: Tao Pan**

An -----(b)(4)----- method is proposed to determine the activity of rhC1INH in ----------(b)(4)----------- drug product.

Information submitted and reviewed included:

3.2.P.4.1. Control of ----(b)(4)-----, Specifications
3.2.P.4.2. Control of ----(b)(4)----, Analytical Procedures
   Quantitative assay of rhC1INH activity
3.2.S.4.3. Control of ----(b)(4)----, Validation of Analytical Procedures
   3.15 rhC1INH activity;
   VAL-P-03-020 Performance qualification report for quantitative rHC1INH activity assay;
   VAL-R-03-026 Performance qualification report for quantitative rHC1INH activity assay;
   VAL-R-03-020 addenda Performance qualification report for quantitative rHC1INH activity assay;
   VAL-R-03-026.A01 Addendum Performance qualification report for quantitative rHC1INH activity assay;
   TRF-R-03-030 Report of the method transfer of rhC1INH activity assay Pharming to ----(b)(4)----;
   TRF-R-03-057 Transfer of the -----(b)(4)----- Assay for the Determination of rhC1INH activity to ----(b)(4)---- to Support ---(b)(4)--- testing of rhC1INH;
   TRF-P-03-012 Transfer protocol of the ----(b)(4)---- assay for determination of rhC1INH activity;
   TRF-R-03-043 Transfer report of the ---(b)(4)--- assay for the determination of rhC1INH activity;
   TRF-R-03-043.A01 Addendum to the Transfer report of the ---(b)(4)--- assay for the determination of rhC1INH activity
3.2.P.5.2. Control of Drug Product, Analytical Procedures
3.2.P.5.3 Control of Drug Product, Validation of Analytical Procedures

In this BLA submission, rhC1INH activity was determined for the release of ---------(b)(4)------------------------- drug product, and also for the stability testing of the ------(b)(4)--------- drug product. The specification was set at ----(b)(4)---- for ----------(b)(4)------------ drug product

(after reconstitution in sterile water). An ------(b)(4)------- method was used to determine the rhC1INH activity, and this method was validated as a quantitative assay.

Method:
To quantitatively determine rhC1INH activity, -----------------------------------------------------------
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-----------------------------------------------------(b)(4)---------------------------------------------------
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(b)(4)--------------------------------------------------------------------------------------------------------
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In this submission, the sponsor provided sufficient information on the assay procedures, including the preparation for controls, standards and samples, measuring steps, and the calculation of reportable result; the sponsor also adequately defined the assay validity criteria.

Validation
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(b)(4)--------------------------------------------------------------------------------------------------------
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Based on the validation protocols and validation reports provided by the sponsor, it can be concluded that appropriate parameters were selected for the validation of the rhC1INH activity assay, the acceptance criteria were met in the validation study, and the assay was validated for its intended purpose.

Assay Transfer

In this submission, it has been indicated that the assay has been successfully transferred to several different labs since its validation, and the related assay transfer reports were also attached for the evaluation of these transfers. The assay transfers were from Pharming, the donor laboratory, to recipient labs, such as ----------------------------------------------------------------------
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------------------------------------------------------(b)(4)-----------------------------------------------
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**Conclusion:**
This method is validated by the sponsor as a quantitative assay for the determination of rhC1INH activity in ----------(b)(4)--------- drug product. The method is clearly written, the selection of validation parameters is appropriate, the acceptance criteria were met, and the assay is suitable for its intended use.

Additionally, based on the assay transfer protocols and reports, it has been demonstrated that the assay has been successfully transferred from Pharming to other labs, such as ---------------------------(b)(4)----------------------------------------------------------------; and the method is approvable for use in these above mentioned labs for lot release ------------(b)(4)-------------- testing.

## 2) Purity and Determination of --------(b)(4)------------
## Reviewer: Mark Levi

Information submitted and reviewed included:

- Module 3.2.S.4.2-Appendix 19-Purity determination by means of (b)(4)
- Module 3.2.S.4.2-Appendix 20-Determination of ---(b)(4)--- in rhC1INH by means of (b)(4)

  Module 3.2.S.4.3-VAL-R-03-123 Validation report for the quantification of ---(b)(4)--- in rhC1INH ------(b)(4)------- drug product
- Response to CMC Questions – 15 Oct 2013

Method

This method is used as a purity assay for the --------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------(b)(4)------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------- -----.

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

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

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

Validation

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

Redact 1 page (b)(4)

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-------------------------------------------------(b)(4)--------------------------------------------------
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--------------------------------------------------------------(b)(4)-------------------------------------
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---------------------------------------------------------(b)(4)------------------------------------
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Information Request-Submitted on 17 and 20 Sept. 2013

a.  In section 6 on page 4 of 6 of Appendix 19, please submit the --------------------(b)(4)--------
    ----------------------- and add a maximum value or range for the -----(b)(4)------ as an
    additional system suitability criterion.

    Pharming's Response (15 October 2013):  -----------------------------------------------------------
    -----(b)(4)----------------------------------------------------------------------------------.
    The sponsor proposed a ---------------(b)(4)----------------- as a system suitability criterion
    And the criterion was added to the system suitability assessment

    Review of Response:  The range is acceptable.

b.  Please provide the ----------------------------(b)(4)------------------------------------------ assay.

    Pharming's Response (15 October 2013):  Data for the past -------------------------------------
    ------------------------------------------------------------------------------------------------
    -----------(b)(4)-------------------------------------------------------------------------------
    ----------------------------------------.

Review of Response:  The response submitted is acceptable.

c.  Linearity of ------(b)(4)------- was validated in VAL-R-03-123. For -----(b)(4)-----, please provide linearity data.

Pharming's Response (15 October 2013):  ----(b)(4)---- rhC1INH was prepared by ---------- ----------------------------------------------------------------------------------------------------- ----------------------------------------------------------------------------------------------------- ------------------------------------------------(b)(4)------------------------------------------------ ----------------------------------------------------------------------------------------------------- --------------------------------------------------------- curve parameters for slope, intercept, and correlation coefficient were determined.  The r value was (b)(4) indicating linearity in the concentration range of the calibration curve.

Review of Response:  Examination and comparison of the slope, intercept, and correlation coefficient of both --------(b)(4)----------- curves indicated linearity.

**Conclusion:**

The method of analysis is reasonable, and the assay validation is satisfactory.


**3)  Water Content by --------(b)(4)---------
   Reviewer:  Ritu Agarwal**

This is an electronic submission. Information submitted and reviewed included:

- 125495/0 – Cover letter, dated 15 April 2013
- 125495/0 – 3.2.P.5.1 Control of Drug Product "Specification"
- 125495/0 – 3.2.P.5.4 Batch Analyses
- 125495/0 – Application - Original BLA: ---------------(b)(4)--------------------
- 125495/0 – 3.2.P.5.2 Analytical Procedure – Water content determination using ---(b)(4)---
- 125495/0 – 3.2.P.5.3 Validation of Analytical Procedure – Water content determination using ---(b)(4)---
- 125495/0.13 – 1.11.1 Quality Information Amendment; Response to IR dated 17 September 2013; Received 15 October 2013
-125495/0.13 – 1.11.1 Quality Information Amendment; Response to IR dated 17 September 2013- Appendix 6, Validation protocol, document VAL-P-03-162.


The moisture content in the C1 Esterase Inhibitor lyophilized drug product is determined using ---(b)(4)--- method. The drug product specification is (b)(4) for both release and stability testing.

Method

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------------------------------------------------------(b)(4)-----------------------------------------------------
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<u>Validation</u>
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--------------------------------------------------(b)(4)---------------------------------------------------------
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<u>Assay Transfer</u>
The ---(b)(4)--- method was transferred between ---------------(b)(4)-------------------------. The
performance of the method was evaluated by --------------------------------------------------------------
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--------------------------------------------------(b)(4)---------------------------------------------------------
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---------------------------------------------------------------------. No statistical analysis was performed
to show the equivalence of results obtained at the -(b)(4)-. It is concluded that the method was
not adequately validated, and the transfer was not successful. In response to CBER IR, sponsor
has clarified that the method is now only performed at --------(b)(4)----------

<u>Information Request</u>
The following IR was submitted on 17 September 2013. The response by Pharming group, NV
of 15 October 2013, follows each request item.

**a.** Page 4 (section 6) of your SOP (Appendix 6), states "that SST solution must comply with
the criteria of the control chart of the moisture (b)(4)". Please provide the details of the
control chart.

<u>Sponsor's Response</u>
For clarity, the water determination method is no longer performed at ---(b)(4)--- and is
only performed at -----(b)(4)------. The analytical procedure as conducted at ----------(b)(4)--
----------, however, uses SST criteria as requested in question 3b below. Therefore, the
statement "that SST solution must comply with the criteria of the control chart of the
moisture (b)(4)" has been replaced by: "The water standard --------------------------------------
--(b)(4)----------------------------------------- (relative against the value on the standard's
Certificate of Analysis [Appendix 5]): 97.5 –102.5." The analytical method has been
revised accordingly (see Appendix 6 of 3.2.P.5.2).

b. The test method (Appendix 6) does not include the assay acceptance criteria. Please revise
to include at minimum acceptable RSD or SD of the (b)(4) determinations and acceptable
deviation from the mean of the result for --(b)(4)-- sample determinations and resubmit for

review.

Sponsor's Response

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


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




-------------------------------------------------------------------------------(b)(4)------------------------
----------------------------------------- of this method will be determined in the validation study
described in the Sponsor's response to Questions 3c, d and e. The Sponsor will update the
method to include a requirement for an R value for ---(b)(4)--- sample results once the
validation has been completed.

c.  The method validation was performed by outsourced laboratories (------(b)(4)------), and
    then transferred to ----(b)(4)---- for further validation. The method validation by -------------
    -(b)(4)-------- was attached as Appendix A. Appendix A included the comparison of sample
    preparation with ------------------------(b)(4)-------------------------. The validation design
    and results were not submitted. Please submit complete validation design, and results for
    the   specificity, accuracy, repeatability, linearity, range and robustness studies.

d.  The reproducibility and intermediate precision studies (Appendix B of Module3.2.P.5.3)
    performed as part of the method transfer report were executed at only --------------------------
    --(b)(4)--------------------- analyses using (b)(4) batches of the sample --------(b)(4)----------
    at -------(b)(4)--------- levels across the assay range, and submit the data for review.

e.  The results of intermediate precision (Appendix B) did not meet the acceptance criteria, yet
    section 4.2.3 of this Appendix states that, "the unknown sample variance seems to play a
    major role in the experiment. Because the precision at ----(b)(4)---- is on the same level or
    even better than the ---(b)(4)---, it is justifiable to conclude that intermediate precision is
    acceptable". This argument is not acceptable. Please provide data to show that the

intermediate precision results met the acceptance criteria.

Sponsor's Response to Questions c, d and e
A formal validation was not conducted based on the assay being a ---(b)(4)--- method; therefore we considered the method transfer and the limited validation of the method adjustment as being satisfactory at the time. However, we commit to performing a validation.  As requested, our validation design can be found in (Appendix 6). We will submit the validation report no later than 22 November 2013.

Evaluation: The response to IR's is satisfactory.

Conclusion: The method is described in sufficient details and incorporated appropriate assay validity criteria. The validation protocol is adequately described. The review could not be completed due to the pending validation report.

**Status:**  As of 01/02/14 the Validation Report has not been received.  It is requested that the sponsor submit the report to allow the evaluation of the adequacy of this procedure.

4)  **"---------------------------(b)(4)---------------------------------------- rhC1INH" assay
     Reviewer:  H. Wang**

Information submitted and reviewed included:

- 3.2.P.5.1 DP Specification
- 3.2.P.5.4 Batch analyses
- 3.2.P.5.2 Analytical procedures
- 3.2.S.4.2 Appendix 27: SOP "Limit test for ----------------------------------------(b)(4)------------- --------- by means of (b)(4)"
- 3.2.S.4.3 Validation of analytical procedures (---(b)(4)---) Section 4.1 ------------------------------ ----(b)(4)--------------------------
- 3.2.S.4.3 Validation of analytical procedures (---(b)(4)---) Section 4.1 ------------------------------ ----(b)(4)--------------------------
- VAL-R-03-092 Validation report of the (b)(4) method for detecting ------------------------------- ----(b)(4)---------------------------------------------- in vialed product
- Amendment 0.13 including the updated SOP

Method
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-----------------------------(b)(4)-------------------------------------------------------------------------
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Validation
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--------------------------------------------(b)(4)------------------------------------------------------
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--------------(b)(4)-------------------------------------------------------------------------------------
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-------------------------------------------------------------------------(b)(4)----------------------------
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Information Requests
After initial review of the SOP and the validation report, eight IR items regarding this assay
were sent to the sponsor through RPM on 9/17/2013. The responses were received on
10/15/2013 in the amendment 13. In the same amendment, an updated SOP is submitted
(3.2.S.4.2 – Appendix 27).

a.  Please clarify if percentages of impurities are calculated by -------------------------------(b)(4)----
------------------------------------------------------ in the section 5: "Data Analysis and
Calculations" of the SOP "Limit test for --------------------------------------------(b)(4)----------------
-------------- by means of (b)(4)".

Response from Pharming Group NV: The Sponsor confirms that percentages of impurities are
calculated by -----------------------------------------------------------------(b)(4)----------------------
--------------------------. This is indicated in 3.2.S.4.2 Appendix 27 section 5 by referring to

"-----(b)(4)----" and is also indicated in 3.2.S.4.2 Appendix 27 section 7 where the result is reported as --------------------(b)(4)----------------------.

Review of the response: The -------------------(b)(4)--------------------- calculation is not specified in either the section 5 or the section 7 of the SOP. The SOP needs to be revised at least for section 5 (DATA ANALYSIS AND CALCULATIONS).

b.  Please add acceptance criteria for --(b)(4)-- performance parameters such as ----------------------
--(b)(4)---------------------- as system suitability criteria in section 6: "System Suitability Assessment" to the SOP "Limit test for -------------------------------(b)(4)----------------------------
-------- by means of (b)(4)" and resubmit the SOP for review.

Response from Pharming Group NV: For system suitability testing (SST) ------------------------------
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-------------------------------------------------------------------------------------------(b)(4)---------
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------------(b)(4)----------------------------------------------------------------------------------------
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------------------------------------------------------------------------------.

The analytical method has been revised accordingly (see 3.2.S.4.2 Appendix 27).

Review of the response: It is acceptable to use the --------------------------------------------------------
--(b)(4)----------------------------------------------------------. However, the criteria suggested in the response are not set properly.  The criteria should take into account the -----------------------
------(b)(4)------------------------------------------ and give indication for the need of -------------------
--(b)(4)--------. CBER requests a --------------------------------(b)(4)----------------------------. The SOP needs to be revised.

c.  It is stated in section 6 of the SOP "Limit test for ------------------------------------(b)(4)-----------
---------------------- by means of (b)(4)":
"--------------------------------------------------------------------------------------------------------
-------------------------------------------------------------------------------------------*(b)(4)*---------
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---------------------------------------------------------------------------------------------- "
Please give the percentage of ----(b)(4)---- based on your historical data for this assay.

Response from Pharming Group NV: No ---(b)(4)--- has been rejected to date. ----(b)(4)---- has used the same -(b)(4)-- since the introduction of the test method and have performed more than --------------------------------(b)(4)--------------------------------------------------were qualified for use ----(b)(4)---- were rejected.

Review of the response: The response is satisfactory.

d.  In the VAL-R-03-092: "Validation report of the (b)(4) method for detecting ----------------------
---------(b)(4)------------------------------------------------- in vialed product" (validation report), one  of the specificity study criteria is  "----------------------------------(b)(4)-------------------------
----". However, ----------------------------------------(b)(4)----------------------------------------. The ----(b)(4)---- should be set for -------------------------------------------------------------------------
-------------------------------------------------(b)(4)-----------------------------------------------------------
--------------.  Please revise your SOP to include the -----(b)(4)----- as described above and submit your revised SOP along with supportive data for review.

Response from Pharming Group NV: Requirements for reliable calculation of -------------------------
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-----------------------------------------------(b)(4)-------------------------------------------------------------
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--------------------------------------------------------. The sponsor's response to Question 2(h) illustrates the non-reliability of generating ----------------------------------------------(b)(4)-----------
-------------------------------------------------------------------------.

However, in order to achieve a reliable system suitability parameter, the Sponsor proposes the introduction of a qualitative criterion for the limit test: "-----------------------------------------------
-----------(b)(4)------------------------------------------------------------------------------------------------".
This qualitative SST criterion, together with the already implemented SST criteria, will increase the assurance of detecting ---------------(b)(4)------------- in this limit test. It is also in line with the qualitative acceptance criterion set for the robustness studies during method validation, i.e., "under all tested conditions a ----------------------------------------(b)(4)-------------
-------------------------------" (see 3.2.S.4.3 Appendix 95).

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

The sponsor concludes that, for a limit test, the implementation of a qualitative criterion "----------------------------------------------------------------(b)(4)------------------------------------------------
-----------------------------", together with existing SST criteria ensures that the limit test is

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capable of detecting ------------(b)(4)-------------- even though no baseline resolution is achieved.

Review of the response: Add "------------------------------------------------------------------------(b)(4)--------- ---------------------------------------------------------------------------------." to the section 6 (SYSTEM SUITABILITY ASSESSMENT) of the SOP is not satisfactory. CBER suggests setting a criterion of -------------------(b)(4)----------------------- as part of system suitability parameter to assure sufficient separation between the impurities and main (b)(4). The SOP needs to be revised.

e.  Please identify the (b)(4) which (b)(4) between -------------------(b)(4)------------- with ------------ --------(b)(4)---------------- in the page 38 of 50; (b) ---(b)(4)--- in page 41 of 50 and (c) --- (b)(4)- in page 42 of 50 (Appendix III) of the validation report VAL-R-03-092.  Please provide data to support your identification.

Response from Pharming Group NV: --------------------------------------------------------------------------- -------------------------------------------------------------------------------------------------------------------- -----(b)(4)-------------------------------------------------------------------------------------------------------- -------------------------------------------------------------------------------------------------------------------- -------------------------------------------------------------------------------------------------------------------- ------------------------------------------------------------------------------------------------------------.

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

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

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

Review of the response: The response is not satisfactory. "*The -----(b)(4)------ can either -------(b)(4)--, since it represents a ------------------------(b)(4)-------------------------------------.*" is in the section 6 (SYSTEM SUITABILITY ASSESSMENT) of the SOP. However, the range of retention time of various -------(b)(4)---------- should be given in section 5. The SOP needs to be revised.

f.  Please provide document WI 1231 cited in page 17 of 50 of the validation report VAL-R-03-092.  Provide -----(b)(4)------ for the data in Table 6 on the same page.

Response from Pharming Group NV: Document WI 1231 is provided in Appendix 1 to this response.
------(b)(4)------ for the data (in Table 6 of the validation report VAL-R-03-092) from Day 1 and Day 2 are provided as Appendix 2 and Appendix 3, respectively, to this response. Sample reference codes mA1, mA2, and mA3 refer to the -----(b)(4)----- sample, codes mB1, mB2, and mB3 refer to the sample -----------------(b)(4)-------------------, and codes mC1, mC2, and mC3 refer to the sample -----------------(b)(4)-----------------.

Review of the response: WI 1231 is provided and reviewed. The specifications for this DP are that --------------------------(b)(4)------------------------------. Combined with information provided inVAL-R-03-092, the ---------------------------------------------------------------------------------------------------------------------------------(b)(4)-------------------------------------------------------------------------------------------------------------------------.

Thus, the concentrations of these impurities in the samples analyzed for method validation are higher than your specification limits.  CBER requests the sponsor to provided results of your accuracy study in which the total content of each of these (b)(4) impurities -(b)(4)- is at or below the respective proposed specification limits with recovery and repeatability that are reasonable for a ------(b)(4)----- method for an impurity. The recovery should be in the range --(b)(4)-- and RSD for repeatability should be (b)(4).

g.  Your acceptance criteria for the Robustness study (section 7 of the validation report VAL-R-03-092) is "*Small changes in ---------------------------------------------------------------------------------------(b)(4)---------------------------------------------------- should only have limited influence on the ---(b)(4)---*" (page 3) of the (b)(4).  Please explain what "limited" means and how you determine objectively whether a change is limited or not.

Response from Pharming Group NV: "Limited influence" is objectively determined by the compliance of the method with the acceptance criterion applied during method validation. The criterion, as described in section 7 of the validation report VAL-R-03-092 (3.2.S.4.3 Appendix 95), was: "under all tested conditions, a ---(b)(4)--- should be visible between ------------(b)(4)----------------".

All -----(b)(4)------ showed a visible ----(b)(4)---- between ------------(b)(4)-------------- and hence complied with the validation criterion for robustness. Although a -----(b)(4)----- was visible, ---(b)(4)--- could not always be determined as explained in the Sponsor's response to

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question 2(h). However, the set of System Suitability Tests (SSTs) in this limit test ensures that the assay is capable of yielding reliable reportable results for this limit test.

Review of the response: The response is not acceptable. CBER request is detailed in question d.

h.  Under Robustness study (section 7 of the validation report) you stated that the -----(b)(4)------ could not be determined.  However, effect on (b)(4) is part of your acceptance criteria.  Please explain why your Robustness study results are acceptable as passed.  Furthermore, we do not agree that the ---(b)(4)--- cannot be determined because the -------------(b)(4)-------------- are clearly visible in the -----(b)(4)------ you provided, which in our opinion should permit you to calculate --------------(b)(4)--------------------- using the equation

$$(b)(4)$$

-------------------------------------------------(b)(4)-------------------------------------------------.  Please calculate ------------------------------------------------------------------------------(b)(4)------------------ ---------- used in this study and submit for review.

Response from Pharming Group NV: -------------------------------------------------------------------------- -------------------------------------------------------------------------------------------------------------------- ----------------------------------------------------------(b)(4)---------------------------------------------------- -------------------------------------------------------------------------------------------------------------------- ---------------------------------------------------------------------------------------------------------.

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

$$(b)(4)$$

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

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

To ensure sufficient ---(b)(4)--- between the ---(b)(4)--- and rhC1INH peaks in routine testing, the Sponsor proposes the introduction of a qualitative criterion for the limit test: "---(b)(4)--- must be visible between the ------------------------(b)(4)-----------------, and between the ----------- -----------(b)(4)-----------------------". See also Sponsor's response to Question 2(d).

Review of the response: CBER understands that due to non-baseline ----(b)(4)---- among impurities and main component, the numeric ---(b)(4)--- values between ------------------------------------(b)(4)------------------------------------ may be not reliable as descried in the question d's response. CBER's request is detailed in question d.

<u>Second Information Request</u>

Based on the review of the response to our first IR (Amendment 13), the following IR was sent to the sponsor on 11/06/2013.  A Quality Information Amendment response to the above requests was received from the sponsor on 11/20/13.   The manufacturer's responses follow each item.

1.    Please revise your SOP (3.2.S.4.2 Appendix 27) address the following concerns and submit for review.
- ------------------------(b)(4)--------------------------------- calculation is mentioned in the section 6 (System Suitability Assessment) of the SOP. However, no --------(b)(4)------ is specified in either section 5 (Data Analysis and Calculations) or the section 7 (Reportable Results) of the SOP. Please add appropriate -----------(b)(4)------------ in section 5 of your SOP.
   - o   Response:  Section 5 in Appendix 27 of Module 3.2.S.4.2 has been revised to include the --------------------------(b)(4)---------------------------- calculation.
- It is acceptable to use the ----------------------------------------------------------------------------------(b)(4)---------------------------------------------------. However, we do not agree with the criteria suggested in the response are not set properly.
*"-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------(b)(4)-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------."*
The criteria should reflect change in the --(b)(4)-- performance over time and give indication of the necessity of --(b)(4)-- replacement.  Therefore, the ---(b)(4)--- should have an acceptable lower limit. We suggest the lower limit to be (b)(4).  Please include an appropriate lower limit of the ----(b)(4)---- to your SOP.
   - o   Response:  Section 6 in Appendix 27 of Module 3.2.S.4.2 has been revised to include an acceptable -----------------(b)(4)--------------------.
- *"---(b)(4)--- must be visible between the -------------------(b)(4)----------------------, and between the -----------------(b)(4)----------------."* is added to the section 6 (System Suitability Assessment) of the SOP.  This is subjective and does not permit quantitative assessment of -(b)(4)- performance. If you cannot define a --(b)(4)-- between the (b)(4), as you stated in your response (Amendment 13), please include appropriate quantitative criteria, such as, ----------------------------(b)(4)-----------------, to assess performance to your SOP.
   - o   Response:  Section 6 in Appendix 27 of Module 3.2.S.4.2 has been revised to include a quantitative assessment of -(b)(4)- performance.  The --------(b)(4)-------- for the -----(b)(4)----- and the first -------------------(b)(4)--------------------- and for the last ---------------(b)(4)----------------------- and the rhC1INH (b)(4) must be (b)(4).
- *"The ------(b)(4)------ can either ---(b)(4)---, since it represents ---------------------------------------(b)(4)------------------------------."* was described in the section 6 (System Suitability

Assessment) of the SOP. We think that your SOP should include the range of retention times of -----(b)(4)------- and the result should be reported as the percentage of all ----------------------- -----(b)(4)-------------------------------------------- in section 5 (Data Analysis And Calculations).

      o   Response:  Section 5 in Appendix 27 of Module 3.2.S.4.2 has been revised to include the range of retention times of -------(b)(4)--------, including how to report the result (i.e., as the sum of area percentage of all rhC1INH species).

Evaluation of Responses:  Information regarding changes to the method are acceptable.

2.        Your proposed specifications for the drug product are --------------------------(b)(4)------ -------------------------------- respectively.  However, you have (b)(4) the sample with ------------- ------(b)(4)---------------------------------- in your validation study (VAL-R-03-092).  Thus, the concentrations of these impurities in the samples analyzed for method validation are higher than your specification limits.  Please submit results of your accuracy study in which the total content of each of these (b)(4) impurities after (b)(4) is at or below the respective proposed specification limits with recovery and repeatability that are reasonable for a -----(b)(4)--------- method for an impurity.  We think that your recovery should be in the range ---(b)(4)--- and RSD for repeatability should be (b)(4).

      o   Response:  The request for additional accuracy studies and -(b)(4)- experiments reflects the approach taken for validation of the limit of quantification (LOQ) of a quantitative method.  However, this procedure for determination of the impurities ----------------------------(b)(4)--------------------------------- is currently in use as a limit test and has been validated as such.  The parameters were validated for a limit test according to the ICH Q2(R1) guideline for Specificity and Detection Limit.  Both parameters are covered by the validation study presented in VAL-R-03-092.

           The approach taken during validation of the limit test was based on ICH Q2(R1), determination of LOD based on visual evaluation.  The guidance states: "The detection limit is determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be reliably detected."  This is the approach taken during validation, in which known concentrations of ---------------------(b)(4)-------------------------------- ----------------- were added to a drug product sample.

           As indicated in the initial submission (module 3.2.S.4.3 section 4.1 [sequence 0000]), Pharming is in the process of developing a quantitative assay for determination of the impurities ------------(b)(4)--------------.

Evaluation of Response:  Reliability at the specification criteria has not been adequately demonstrated as -(b)(4)- at the specification levels has been made in addition to amounts of these impurities that were initially present.  As the sponsor has indicated that a quantitative assay is being developed, we recommend that this be adopted for the purpose of better monitoring of product quality and consistency.

    **Conclusion:**  Although reliability at the specification level has not been fully demonstrated, the proposed limits test for the impurities -------------(b)(4)---------------- **is**

acceptable on an interim basis for the approval of this product.  We ask that Pharming commit to the submission of a quantitative assay for the determination of these impurities for the purpose of consistently monitoring these impurities as critical quality attributes of the product.

**5.  ------------------(b)(4)------------------------------------------**
**Reviewer:  Yichuan Xu**

**Submitted Information and Documents:**

Information submitted and reviewed included:
125495/0.0 (Original Application) – April 16, 2013
   3.2. S.4 Control of Drug Substance:
   - Analytical Procedure
     – (b)(4)
   - Validation of Analytical Procedure
     – Validation protocol for the determination of -------------(b)(4)------------------- used for downstream processing
     – Validation of the method for the determination of -------------(b)(4)---------------- used for downstream processing
   125495/0.13 (Amendment) – Oct 15, 2013
     – Response to CMC questions

Method

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--------------------------------------------------------(b)(4)-------------------------------------------------
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Method Validation

The method is used as a quantitative assay for the determination of an impurity.  The following validation characteristics were evaluated: Specificity, Precision (Repeatability and Intermediate Precision), Accuracy, Linearity, Range, Limit of Detection (LOD), Limit of Quantification (LOQ) and Robustness.  The selection of validation characteristics is appropriate and consistent with the recommendations of guidance ICH Q2 (r1) for an impurities assay procedure.

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## Information Request

The following IR was sent to the sponsor on September 17, 2013.

a.  ---------------------------------------------------------------------------(b)(4)--------------------
    ---------------------------------------- show no observable difference.  Please provide data
    on ------------------------------------------------------(b)(4)-----------------------------------------
    ----------------------------------------------.

Pharming's response: -----------------------------------------------------------------------------------
-------------------------------------------------------------------------(b)(4)----------------------
------------------------------------------------------------------.  This is acceptable.

b.  Please provide -----------------------------------------------------------(b)(4)-------------------------
    --------------------- to demonstrate specificity.

Pharming's response: ---------------------------------------------------------------------(b)(4)-----------
----------------------------------------.  Results show that the addition of standard ----------------------
----------(b)(4)-----------------------------------------------------.  The specificity of the method
has been demonstrated.

c.  Section 7.1 of the method validation report (S-144-0575-R-(b)(4)) (page 14), states, "the
    stated requirement for the ------(b)(4)-------------- was not met."  Section 10 recommends
    that the requirement adjust from -----(b)(4)------.  It seems from your results that your
    method development was not complete.  Please complete your method development,
    validate it and submit for review.

Pharming's response:  The response does not adequately address the concern. The following
IR was sent to the sponsor on October 30, 2013.

- In response to our question number 5c on (b)(4) assay, you responded (Amendment
  13), "-------------------------------------------------------------------------------------------
  ----------------------------------------(b)(4)----------------------------------------------------
  -----------------------------." We don't think this statement is necessarily true.  We
  think that this depends upon the ----------------------------(b)(4)------------------------
  --------. Please provide data using an appropriate alternate analytical method (for
  example, (b)(4)) to show that -----------------------------------------------------------------
  -------(b)(4)-----------------------------------------------------------------------------.

  o  A response from Pharming was received 11/20/13.
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**Conclusion:** The response by the sponsor is acceptable in that any contribution of the ---------------------------(b)(4)---------------------------- would result in an overestimation of the quantity of this impurity. The ------------(b)(4)---------- ---------------- method for (b)(4) is acceptable for its intended purpose as a limits impurity test.

**6)** **Determination of the concentration of ---------(b)(4)--------- in rhC1INH using (b)(4)**
**Reviewer:  Yichuan Xu**

3.2.P.5  Control of Drug Products:
- Analytical Procedure
  – Determination of the concentration of -----------(b)(4)-------- in rhC1INH using (b)(4)
- Validation of Analytical Procedure
  – Method Validation Report of the -(b)(4)- method for determining the concentration of --------(b)(4)---------- in rhC1INH
125495/0.13 (Amendment) – Oct 15, 2013
- Response to CMC questions – Oct 15, 2013


<u>Method</u>

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----------------------------------------------. The method validation protocol and method validation report of the assay are included in the submission, which provide sufficient details of the procedure and Method Acceptance Criteria to permit review.

## Method Validation

The method is used as a quantitative assay for the determination of an impurity. The following validation characteristics were evaluated: Specificity, Precision (Repeatability and Intermediate Precision), Accuracy, Linearity, Range, Limit of Detection (LOD), Limit of Quantification (LOQ) and Robustness. The selection of validation characteristics is appropriate and consistent with the recommendations of guidance ICH Q2 (r1).

The Specificity is examined by ---------------------------------------------------------------------------
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**Information Request**

The following IR was sent to the sponsor on September 17, 2013.

a. Please provide data to show linearity of the ------------(b)(4)------------ in sample and that the -----------------(b)(4)----------------------- (regression lines) of samples and that of the standard are parallel.

Pharming's response: The data of sample linearity was provided. The results are summarized in the following table.

(b)(4)

The results in the table show that the ----------------------------------------(b)(4)--------------
----------------, which demonstrate parallelism between two linear fits. The response
adequately addresses the concern.

b.  Your -----(b)(4)-------- (pages 7-9 of VAL-R-03-089) in the validation report show
    some variation in the --------------(b)(4)----------------.  While such variation can be
    normal, please provide -----(b)(4)--------- of a sample solution before and after ---------
    --(b)(4)------------- to demonstrate specificity of the assay.

Pharming's response: The results of a sample solution before and after --------------(b)(4)--
---------------- are provided. The results indicate that the ------------------------------------------
---------(b)(4)-------------------------------------------------------. This is acceptable.

c.  In Section 8 of the method validation report (VAL 1516-0511), the result of Method
    repeatability (RSD% (b)(4)) in page 16 is inconsistent with that presented in the table
    9 (RSD % (b)(4) in page 17).  Please explain.

Pharming's response: The inconsistency in repeatability results in the validation report has
been acknowledged by the CMO and a memo has been written in order to rectify the in
correct RSD value. This is acceptable.

d.  Section 11.1 (page 23 of the method validation report), states, "When varying the -----
    -----------------------------(b)(4)-------------------------------------- according to the
    validation protocol, the variations in ----------------(b)(4)-------------- did not meet the
    acceptance criteria established in the validation protocol. However, those variations
    do not reflect errors that could occur during normal operation." This is not acceptable.
    We conclude that your Robustness failed.  Please redo the Robustness study and
    submit your results for review.

Pharming's response: The response does not adequately address the concern. The
following IR was sent to the sponsor on October 30, 2013.

In reference to your response to our question 4d on the robustness issue, we do not agree
that ------------(b)(4)--------------------- are not critical parameters for a ----------(b)(4)-------
-------- method.  Your own results show that the -------------------------------------(b)(4)--------
---------------------------------, thereby showing that this parameter is critical.  Indeed, you
chose to study these parameters because they are critical.  Please provide data to show that
the --------------------------------------------------------------------------------(b)(4)-----------------
----------------------------------------------------------------.  In addition, please provide data to
show the --------------------------------------------------------------------------------(b)(4)------
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Sponsor's Response
Data showing ------------------------------------------------------------------(b)(4)----------------
------------------------------------- is provided.   A comparison of -------------------------------
-------------------------------------------(b)(4)------------------------------------------------------------
------ is not available, as only samples were tested at the different conditions.

The Sponsor would like to clarify what was meant by "not critical" in the context as written in Module 3.2.S.4.3 section 4.2 [sequence 0000] as: -------------(b)(4)------------------------ tested in the study were not expected to be encountered during the validated operational conditions, and as such were considered "not critical" only within this context for this study. However, the Sponsor acknowledges that the parameters themselves are, of course, critical for any (b)(4) assay. ----------(b)(4)-------------------- was already defined in the assay description. The assay description was modified in the earlier response to Question 4d [sequence 0012] in order to set a -------------------------------------(b)(4)------------------------- --------------------------.

Pharming realises that the robustness study described in the initial submission could have been expanded upon using -----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------(b)(4)----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------.

   **Status:** We recommend that Pharming NV commit to a date for submission of the expanded robustness study as described.

## 7) (b)(4) method for ----(b)(4)---- of rhC1INH --------(b)(4)--------- product
**Reviewer:  A. Del Grosso**

Information submitted and reviewed included:

3.2.P.4.1. Control of ----(b)(4)----, Specifications
3.2.P.4.2. Control of ----(b)(4)----, Analytical Procedures
   * ----(b)(4)---- of recombinant human C1 inhibitor using -------(b)(4)--------
3.2.S.4.3. Control of ----(b)(4)----, Validation of Analytical Procedures
   * Validation Report: (b)(4) method for the -----(b)(4)----- of rhC1INH ------------------(b)(4)----- drug product
   * TRF-P-03-018  Transfer Protocol for the --(b)(4)- method for the ------(b)(4)------ of the rhC1INH ----(b)(4)----
   * TF_-R-03-46 Transfer Report for the --(b)(4)- method for the ------(b)(4)----- of the rhC1INH ----(b)(4)----
   * VAL-R-03-146 Validation of the ---(b)(4)--- method for the -------(b)(4)------ of the rhC1INH -----(b)(4)------
   * VAL-P-03-103 Validation protocol of the --(b)(4)-- method for the -------(b)(4)---- --------- of the rhC1INH ------(b)(4)-------

-----(b)(4)----- is used to confirm the identity of rhC1INH glycoprotein based on correspondence ------------------------------------------------------------------------------------------------------ ------------------------------------------------------------------------------------------------------------------ ----------------------------------------(b)(4)-------------------------------------------------------------- ------------------------------------------------------------------------------------------------------------------ ------------.   According to information submitted in the validation protocol, ----------------------- ------------------------------------------------------------------------------------------------------------------ ------------(b)(4)-------------------------------------------------------------------------------------------- -----------------------------------------------------------------------------------.

Method
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The method description was found to be adequate, in sufficient detail to permit replication and incorporated adequate system suitability specifications.

Validation
The method was validated as an Identification test.  Per the ICH-Q2(R1) guidance, recommended analytical characteristics for evaluation are specificity and robustness. Characteristics evaluated by Pharming were Specificity and Robustness as well as Precision. In the evaluation of specificity it was demonstrated that excipients in the rhC1INH -----(b)(4)-- ----------------- sample and reagents used in the method do not interfere with the ----(b)(4)----- quantitation.

Robustness was evaluated with respect to the following factors:
- --------------(b)(4)----------------------------
- -----------------------------(b)(4)------------------------------------
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**Conclusion:** The ------------(b)(4)----------- procedure has been adequately described and validated for use as an Identification method for the rhC1INH ----------(b)(4)--------- drug product.

### 8) rH-C11NH host related impurities (b)(4) assay.
### Reviewer:  Noel Baichoo

Information submitted and reviewed included:

- 125495/0-3.2.S.4.3 Validation of Analytical Procedures-Report, document number VAL-R-03-027: Performance qualification report for the rH-C11NH host related impurities (b)(4) assay.
- 125495/0-3.2.S.4.3 Validation of Analytical Procedures-Report, document number TRF -R-03-006: Report of the method transfer of HRI (b)(4) for rHC11NH from Pharming to ---(b)(4)-------------

- 125495/0-3.2.S.4.3 Validation of Analytical Procedures-Report, document number TRF-R-03-042: Transfer report of the -(b)(4)- assay for determination of host related impurities from ------------------------------(b)(4)------------------------------.
- 125495/03.2.S.4.2 Analytical Procedures-Protocol Appendix-24-(b)(4) for the detection of Host Related Impurities (HRI)
- 125495/0-3.2.S.4.3 Validation of Analytical Procedures-Protocol, document number TRF-P-03-018: Transfer protocol of the (b)(4) assay for determination of host-related impurities
- 125495/0.13 1.11.1 Quality Information Amendment –Protocol - Appendix 9- Validation Protocol, document number PQP746 – Performance Qualification Protocol for the rh-C1INH Host related impurities (b)(4) assay

  **----(b)(4)----**
- 125495/0-3.2.S4.3 Validation of Analytical Procedures-Report, document number  VAL-R-03-033: Performance qualification report for qualitativerH-C1INH ---(b)(4)--- assay.
- 125495/0-3.2.S4.3 Validation of Analytical Procedures- Report, document number VAL-R-03-033.A01: Addendum Performance qualification report for qualitative rH-C1INH ---(b)(4)--- assay.
- 125495/0-3.2.S4.3 Validation of Analytical Procedures-Report, document number VAL-R-03-157: ---(b)(4)--- rhC11NH: additional validation study report on migration distance.
- 125495/0-3.2.S4.3 Validation of Analytical Procedures-Report, document number TRF-R-03-039:Transfer report of the ---(b)(4)--- assay for determination of protein profile
- 125495/0-3.2.S4.3 Validation of Analytical Procedures-Report, document number TRF-R-03-024: Transfer report of the ---(b)(4)--- method for identity determination of rhC1INH from Pharming to ----(b)(4)----
- 125495/0-3.2.S.4.2 Analytical Procedures-Protocol Appendix 16- SOP for Identity test with ----------(b)(4)----------
- 125495/0-3.2.S4.3 Validation of Analytical Procedures-Protocol, document number  VAL-P-03-021: Performance qualification protocol for qualitative rH-C1INH ---(b)(4)--- assay
- 125495/0-3.2.S4.3 Validation of Analytical Procedures-Protocol, document number VAL-P-03-021.A01: Performance qualification report for qualitative rH-C1INH
  ---(b)(4)--- assay – Addendum
  - 125495/0-3.2.S.4.3 Validation of Analytical Procedures-Protocol, document number
  TRF-P-03-015: Transfer protocol of the ---(b)(4)--- assay for determination of protein profile

**(b)(4)**

**a. Detection and quantification of Host related impurities (HRl's)" --------------------------------(b)(4)------------- purified rH-C1INH samples**

Method
The proposed assay to identify and quantify residual HRI's is a --------------------------------------
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Information Request

The protocol described in Validation Report VAL-R- 03-027 was not submitted with the original BLA submission. We submitted an Information Request (IR) on 9/17/2013 which included a request for this information. The response to the IR received on 10/15/2013 (125495/0.13 1.11.1) contained the protocol.

**Conclusion:**  The response to our information request is adequate.  The described (b)(4) procedure for host related impurities (HRl's)" in ------------(b)(4)------------ purified rH-C1INH samples is acceptable for its intended use.

**---(b)(4)----**
**b.  Determination of identity of rH-C1INH by qualitative ---(b)(4)---**

Method
The proposed method to identify rH-C1INH is based on ----------------------------------------------
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Method Validation
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The following Information requests were submitted by CBER on 11/06/13. The manufacturer's response made on 11/20/13 follows each item.

a.   Please explain the use of ------------------------------------------------------------------------------
-------------------------------------------(b)(4)------------------------------------------------------
----------------------------------------------------------------.

In section 8 of TRF-R-03-039 there are deviations due to failure of the -----(b)(4)-----. You stated, "Testing at (b)(4) of several other lot numbers of the protein molecular weight -----------
-(b)(4)- revealed the same problem (data not shown). Since there was no ---(b)(4)-- available it was decided to proceed with the ---------------(b)(4)-----------------." In section 8 it is stated that -----------------(b)(4)------------------------------------------. Has this been done? Please provide data using different ---(b)(4)---?

Response: During assay development, a commercially available, ----------------------------------------
---(b)(4)------------------------------------ for identity testing of rhC1INH batches in QC release. -
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The differences in quality amongst lots of the ---------------------------------------------------------------
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------------------------------------(b)(4)-------------------------------------------------

b.   You have indicated that the acceptable range of MW in document VAL-R-03-033 to be ---
(b)(4)---.  However, in document TRF-R-03-024 you indicated the same range to be -------------
-------------------(b)(4)------------------------.  The acceptable ranges are significantly different in
these two documents.  Please clarify what the true acceptable range of MW is.  The
specification in the proposed BLA is ------(b)(4)----- of the Rf of the standard.  How does the
specification relate to MW stated in these documents?

   Response:  In QC release testing, the acceptable system suitability range for the migration of
   the rhC1INH reference standard is --(b)(4)--. The range is defined by -----------------------------
   ---------------------------------------------(b)(4)-------------------------------------------------------
   --------------------------------------------------------------------------------------. The analytical
   procedure implemented for QC release testing resulted from the validation study reported in
   TRF-R-03-024. The previously documented range of -----(b)(4)----- (VAL-R-03-033) was
   applied as acceptance criterion for the --------------(b)(4)-------------- of the rhC1INH protein
   band.

c.   This assay is for identity of -----------------(b)(4)--------------------------------------------------------
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-------------------------------------------------------- should be used in addition to demonstrate
identity.  Please indicate if any other method(s) was used to complement identification by ---
(b)(4)--- and provide data.

   Response:  Characterization analysis for identity of rhC1INH batches by various techniques
   is described in Module 3.2.S.3.1 [sequence 0000]. The techniques used for characterization
   analysis for identity included:
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      • ------------(b)(4)-------------------
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**Conclusion:** The responses to CBER's information request are found to be adequate. The assay for Determination of identity of rH-C1INH by qualitative -----(b)(4)---- is acceptable for its intended use.