

DATE: December 5, 2008
FROM: Omer I Butt, CBER/DH, HFM – 343
THROUGH: Felice D’Agnillo, LBVB/DH, HFM-343
Abdu Alayash , LBVB/DH, HFM- 343
TO: Nannette Cagungun, HFM-380
SPONSOR: CSL Behring GmbH.
PRODUCT: C1 Esterase Inhibitor, Human.
TYPE: BLA/Original Application
STN: 125287/0.0

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

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

The pre-defined acceptance criterion was that the reduction of the specific C1-INH activity should not be more than -b(4)-. All data provided shows that the results comply with this acceptance criterion.

Validation was carried out for a storage temperature of --b(4)-- for --b(4)--. A decrease in C1 INH activity of -b(4)- was observed after b(4) hours, and an increase of -b(4)- when challenging conditions of ---b(4)--- were used for the b(4) hour time period. Both data show no significance with a 95% confidence interval.

Drug Product –

Presentation	Storage Period	Condition
--------------	----------------	-----------

Presentation	Storage Period	Condition
Finished Product (Unopened)	30 months	2-25 oC / -b(4)- Relative Humidity
Reconstituted Product	8 hours	2-25 oC / -b(4)- Relative Humidity

Parameters Tested

Test (Analytical Method)	Specification
Appearance	Colorless & clear solution
Dissolution Time	---b(4)-----
Activity (---b(4)-----)	---b(4)-----
Protein (----- b(4)----- --)	--b(4)-----
Residual moisture (----b(4)----- ---)	--b(4)-----
pH (-----b(4)-----)	--b(4)--
Sterility test (membrane filtration)	Sterile, Specification CFR/--b(4)--
Pyrogen test (test in rabbits, calculations)	Pyrogen Free, Specification CFR/--b(4)--
Abnormal toxicity (test in guinea pigs)	Specification CFR/-b(4)-

To meet US requirements, addition tests were carried out –

[b(4)]

The three lots tested for stability of the products are -----b(4)-----.

All three lots have been termed “Lots from Full Scale Process Validation”.

Based on the data from the tested lots, the stability of the product was confirmed for a period of -b(4)- months when stored at -b(4)- and also --b(4)---. Reconstitution of the product did not affect the activity of the product for a period of -b(4)- hours at -b(4)- relative humidity.

No data available for conformance lots.

Water for Injection-

Water for injection has been produced at the sponsors manufacturing site and has been marked with a shelf-life of b(4) months. Studies 112-F10, 110-2003-FS and 110-006 cover the period of b(4)- months for the stability of the water.

Parameters tested for the stability are as below

- -----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)-----

Stability data has been obtained from a total of b(4) lots, with b(4) follow up batches of the filling sized -----b(4)----- . An addition batch of the -b(4)- filling size has been stored at ---b(4)---

b(4) batches of the filling size --b(4)----- have been stored at ----b(4)-----, along with an accelerated condition of ---b(4)-----.

All observed values of all analyzed lots at the long term and accelerated storage conditions are within the specifications according to sponsor. Two of the stability studies for the water for injection, 110-2003-FS and 110-006 are currently ongoing and will continue up to b(4) months. No commitment has been provided for the post-approval stability of these batches.

Post-Approval Stability Commitment –

A pos-marketing stability commitment has been proposed for the finished product for long term storage of ----b(4)-----.

There is an ongoing study for the stability of water for injection. No commitment has been provided for this study.

Amendment – Response to CBER Requests – Submitted 30 th October, 2008-

Additional stability data was provided, which included the European stability protocol for Berinert Lot -----b(4)----- . Data provided meets the standards for the European protocol, and covers a period of up to -b(4)- months.

A -b(4)- month testing period has been setup by the sponsor to complete the stability testing for a second lot, No. ----b(4)----- . The above mentioned 4 US test requirements were not included in the protocol.

Letter Ready Comments-

1. Please provide stability data based on the modified stability protocol that includes the additional stability indicating tests; -----b(4)-----
