DEPARTMENT OF HEALTH & HUMAN SERVICES **Public Health Service**

Memorandum
Food and Drug Administration
Center for Biologics Evaluation and Research
Bethesda, MD 20892

Date : June 20, 2003

From : Patrick G. Swann, Ph.D., Division of Monoclonal Antibodies, CBER, N29B, HFM –555; 301-827-0728; swannp@cber.fda.gov

To : File

Through : Keith O. Webber, Ph.D., Division Director, Division of Monoclonal Antibodies, HFM -555

Subject : : STN 103976 (BLA 99-2748)

Date of BLA submission:	02-JUNE-00
Date received by FDA:	05-JUNE-00
Application filing letter:	25-AUG-00
Standard Decision date:	26-APR-01
New date w/ major amendment:	26-JULY-01
Complete Response Letter:	05-JULY-01
Class 2 Resubmission:	20-DEC-2002
Action Due:	21-JUNE-03

Therapeutic: Recombinant humanized monoclonal antibody (IgG1K) that binds to human IgE. The tradename is 'Xolair'; the USAN name is 'omalizumab'; the investigational name is rhuMAb-E25.

Manufacturer: Genentech
1 DNA Way
South San Francisco, CA 94080-4990

Sponsor contact: Susan Vermeir, 650-225-3316. For CMC issues, the sponsor contact is John O'Connor @ 650-225-2045 or Terry Milby @650-225-2301

Indications: Xolair is indicated for adults and adolescents (12 years of age and above) with moderate to severe persistent asthma who are inadequately controlled with inhaled corticosteroids and have a positive skin test or in vitro reactivity to a perennial aeroallergen. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients. Safety and efficacy have not been established in other allergic conditions.

The following is my review of CMC product information included in the BLA. The paper copy of the BLA is partially replicated by an electronic document (computer-assisted license application or CALA). In addition, the CALA contains batch records from SSF and ----------. This review document contains text and figures copied from the CALA. Potentially proprietary information in my review is limited to the attachments.

List of documents reviewed:

Original submission:

a. Application form 356h date of submission is June 2, 2000. I received a hardcopy of Item 4 on June 6, 2000. The electronic version on CD-ROM was defective. A non-defective CD-ROM copy was delivered to me on June 21, 2000.
b. I requested final virus clearance study reports on July 21, 2000; they were shipped on July 24, 2000; and I received a copy from Kay on August 8, 2000.
c. ---------- conformance lot data (electronic version) were received September 15, 2000.
d. A formal information request was officially sent on October 13, 2000. Additional information requests were sent on November 3, 2000 and December 15, 2000. Reply to all three of these information requests was submitted on February 13, 2001.
e. Manufacturing information obtained during inspection 2/26/01 – 3/9/01.

Resubmission:

f. Application form 356h date of submission is December 18, 2002. STN – 103976-0.011
g. Amendment 12 (submitted December 31, 2002) describes a modification of the final vial to implement a change ----------.
h. Amendment 16 (submitted March 20, 2003) supporting an expiration date of ---- months for drug substance.
i. Amendment 18 (submitted May 5, 2003) containing responses to the CMC Discipline Review letter which had been conveyed on April 15, 2003.
j. Amendment 20 (submitted May 5, 2003) containing responses to the CMC Discipline Review letter which had been conveyed on April 15, 2003.
k. Amendment 21 (submitted May 27, 2003) supporting ---------- of bulk drug substance.
l. Amendment 22 (submitted May 29, 2003) providing an updated reponse to the CMC Discipline Review letter.
m. Amendment 23 (submitted June 6, 2003) providing an updated on drug product stability and Certificates of Analysis for ------- drug product qualification lots.
n. Information received by fax, e-mail and telecon on June 9, June 12, June 13 and June 17, 2003.

1. **Physicochemical Characterization of Reference Standard and Qualifying Lots:** (Attachment 1)

{This section should include a characterization of antibody structural integrity, specificity, and potency as described in the Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (PTC, 1997) Section II.B.5.a of (*1*) and Section II.A.2 of Guidance for Industry for the Submission of CMC Information for a Therapeutic Recombinant DNA-Derived Product or a mAb for *In Vivo* Use (CMCDNA) (*2*)}.

From presentation at the 2000 AAAI meeting by Paula Jardieu of Genentech:

"…a murine monoclonal antibody (--------) directed against IgE was identified which had all of the properties necessary to interfere with IgE responses, but lacked the harmful side-effects of inducing receptor crosslinking. The antibody was selected based on its ability to bind circulating IgE at the same site as the high affinity receptor, thus block binding of IgE to mast cells and basophils. To avoid the problems of antigenicity associated with chronic administration of murine antibodies -------- was humanized. The critical amino acids responsible for the binding of the murine anti-IgE Mab were engrafted into a human IgG1, such that less than 5% of the resulting antibody remain murine in origin. The best of several humanized variants, version 25 (rhuMAb-E25) was selected since it possessed biological activity comparable to --------."

From the proposed labeling:

The humanized antibody is produced by a mammalian cell (Chinese Hamster Ovary [CHO]) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. *{Trademark}* is a sterile, white, preservative-free, lyophilized powder contained in a single-use vial that is reconstituted with Sterile Water for Injection (SWI), USP, and administered as a subcutaneous (SC) injection. A *{Trademark}* vial contains 202.5 mg of omalizumab, 145.5 mg sucrose, 1.8 mg L-histidine, 2.8 mg L-histidine hydrochloride monohydrate, and 0.5 mg polysorbate 20 and is designed to nominally deliver 150 mg of the lyophilized active substance, omalizumab, upon reconstitution with ----- mL SWI.

2. <u>Manufacturing sections of the BLA</u>

2.1. **History/development of product (Attachment 2)**

{This section should include protein/DNA sequences, vectors used, gene constructs, cloning and establishment of cell lines. Requirements are described in section II.B.1 of PTC (*1*), in Section II.C.3.b.i of CMCDNA (*2*)and in ICH Q5b (*4*)}.

2.2. Cell banking (Attachment 3)

{This section should have all the information on the generation and testing of the master cell bank (MCB) and working cell bank (WCB) as well as limits on the life span of culture and ----------. If the product is made in a DNA transfected cell, testing should include copy number at all stages of the cells' life span. Requirements are described in Section II.C.3.ii of CMCDNA (*2*), Section II.C.1. of PTC (*1*), and Section 2.2 of ICH Q5d (*5*)}

2.3. Cell Culture Process (Attachment4)

{This section should have information on the media components and sources/testing of components of animal/human origin. There should also be a description of the ---------- / fermentor transitions, including sizes and days at each stage, a discussion of the way cells transition from one stage to the next should be included. A listing of the in process testing and specifications should also be included. Requirements are described in CMCDNA (*2*)}

2.4. Downstream processing (Attachment 5)

{This section should include a listing of all ----------]. Requirements are described in Section II.C.3.c of CMCDNA (*2*), Section II.B.4 of PTC (*1*)}.

2.5. Formulation and filling (Attachment 6)

{This section should have details of the formulation buffers and how the product is diluted into the final formulation. Include storage tanks and storage conditions. The filling vial size and stoppering system should be described as well as lyophilization

parameters and controls. If the product is lyophilized include information on the reconstitution buffer. Requirements are described in CMCDNA (*2*)}

2.6. Shipping (Attachment7)

This section should have details on any shipping of intermediates, bulks and final vialed product. The description should include if product is shipped fresh/frozen, storage conditions and temperature controls. The time/temperature in transit should worst case scenarios

3. <u>Preclinical sections</u>

3.1. Rationale for use (Attachment 8)

A general review of the pharmacological basis of anti-IgE therapy can be found in (*6*). The therapeutic efficacy of anti-IgE antibodies is attributed to several pharmacological mechanisms: "In addition to the expected effects of these monoclonal antibodies in neutralizing free IgE and inhibiting IgE production by B cells, several indirect biochemical and cellular effects have been uncovered during the course of the clinical trials. These include the accumulation of potentially beneficial IgE–anti-IgE immune complexes and the downregulation of the high-affinity IgE Fc receptors (FceRI) on basophils and mast cells."

3.2. Potency (Attachment 9)

{Requirements are described in section II.B.5.c of PTC (*1*)and section 2.1.2 of ICH Q6b (*7*)}

4. <u>Validation sections</u>

4.1. Process validation (Attachment 10)

{This section should have information on process validation studies. Guidance can be found in the Guideline on general principles of process validation (*8*). From that document: *"Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics."*}

4.2. Assay validation (Attachment 11)

{Requirements are described in ICH Q2a and Q2b (*9;10*)}

4.3. ---------- lifetime validation (Attachment 12)

{From PTC (*1*) "Limits should be prospectively set on the number of times a purification component (e.g. a chromatography ---------) can be reused. Such limits should be based upon actual data obtained by monitoring the component's performance over time."}

4.4. Hold time validation (Attachment 13)

{From ICH Q5c (*11*): "During manufacture of biotechnological/biological products, the quality and control of certain intermediates may be critical to the production of the final product. In general, the manufacturer should identify intermediates and generate in-house data and process limits that assure their stability within the bounds of the developed process." These intermediates could be buffers, process intermediates or purified bulk.}

4.5. Viral clearance studies (Attachment 14)

{Requirements as described in ICH Q5a.: (*12*)}

4.6. Shipping (Attachment 15)

5. Reference Standards and Comparability (Attachment 16)

6. Stability Assays (Attachment 17)

{Guidance can be found in ICH Q5c: Quality of Biotechnological Products: Stability Testing of Biotechnological / Biological Products (*1;11*)}.

7. Stability - Support for dating period (Attachment 18)

{Stability/sterility of drug substance and reconstituted product (to support labeled holding periods) dating periods of diluents}

8. Release tests and specifications:

{Guidance can be found in ICH Q6b: Specifications, Test Procedures and Acceptance Criteria for Biotechnological / Biological Products (*4*)}

8.1. Bulk (Attachment 19)

8.2. Final product (Attachment 20)

9. Miscellaneous listings

9.1. Environmental Assessment

As specified in regulation at 21 CFR Section 25.15(d), Genentech states that the original Xolair BLA (Reference No. BL 103976/0) qualifies for categorical exclusion from the Environmental Assessment (EA) requirement. Specifically, under 21 CFR Section 25.31(c), any action on an NDA, abbreviated application, application for marketing approval of biologic product, or supplement to these applications is categorically excluded and ordinarily does not require the preparation of an EA or an Environmental Impact Statement for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

9.2. Products used in manufacture of significance (Attachment 21)

10. Final conclusions and recommendations

The data submitted in this application support the conclusion that the manufacture of omalizumab (Xolair™) is well controlled and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents in a way that meets or exceeds the parameters recommended by FDA. The conditions used in manufacturing have been validated and a consistent product is produced from different production runs. I recommend approval of this product for human use (under conditions specified in the package insert).

11. Referenced master files (Attachment 23)

12. Literature References

1. Food and Drug Administration (1997) *Federal Register 62*, 9196.

2. CBER and CDER. Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls Information for a Therapeutic Recombinant DNA-derived Product or Monoclonal Antibody for In Vivo Use. 1996.

3. ----------

4. Food and Drug Administration (1996) *Federal Register 61*, 7006-7008.

5. Food and Drug Administration (1998) *Federal Register 63*, 50244-50249.

6. ----------.

7. Food and Drug Administration (1999) *Federal Register 64*, 44928-44935.

8. CDER, CBER, and CDRH. Guideline on general principles of process validation. 1987.

9. Food and Drug Administration (1995) *Federal Register 60*, 11260-11262.

10. Food and Drug Administration (1997) *Federal Register 62*, 27464-27467.

11. Food and Drug Administration (1996) *Federal Register 61*, 36465-36469.

12. Food and Drug Administration (1998) *Federal Register 63*, 51074-51084.

13. ----------.

14. ----------

15. ----------.

16. ----------.

Attachment 1 Physicochemical Characterization of Reference Standard and Qualifying Lots (Characterization)

From Item 4.A.2, Drug Substance; 4.A.2.a.2, Physicochemical Characterization / Proof of Structure (Reference Standard and Qualifying Lots). Reference material for Phase III production process is Lot No. ---------- which was prepared by ----------

The following Lot geneology table was faxed at my request:

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Attachment 2 History/development of product:. (History)

a. Source, name, and characterization of the parent cell line

From Item 4.A.2.c.3

The CHO cell line was developed by Dr. T. Puck, University of Colorado, from a biopsy sample from an adult Chinese hamster, *Cricetulus griseus*. [

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Attachment 3 Cell banking.: (Banking)

Generation

In preparation of the ---------- ampoules of the prebank, ----------, were thawed, cultured in the presence of ---------- and expanded in ----------
The resulting ------- liters of cell ---------- were harvested, resuspended in ---------- pooled, and distributed at a final concentration of approximately ---------- ampoules. After integrity testing, --------- intact ampoules were frozen to ——— using a controlled rate ---------- and transferred to storage in ----------

In preparation of the rhuMAb E25--- WCB, Cell No. ---------- ampoules of the MCB, ---------- MSB, Cell No. ---------, were thawed, cultured in the presence of ---------- and expanded in ----------
The resulting ---------- of cell suspension were harvested, resuspended in ---------- pooled, and distributed at a final concentration of approximately ---------- ampoules. After integrity testing, ----- intact ampoules were frozen to ––––––C using a controlled rate ---------- and transferred to storage in ----------

Characterization and Testing

The MCB and the WCB were characterized using a battery of biochemical, biological, and immunological tests that are known to detect bacterial, mycoplasmal, fungal, or viral agents, which may be associated with mammalian cell culture. These tests were chosen to detect agents transmitted either horizontally by infection (adventitious) or vertically by genetic inheritance (endogenous). Each test method is described below. Refer to Table 5 for a summary of the MCB No. --------- and WCB No. ---------- specifications, test results, and study numbers.

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1) To assess freedom from contamination by bacteria and fungi, MCB cells were evaluated for microbial content using the ----------. The MCB showed no detectable bacterial or fungal contamination.

   Studies evaluating WCB cells were performed as described under MCB… The WCB showed no detectable bacterial or fungal contamination

2) Testing was done by standard methods that detect the presence of ---------- mycoplasma.[

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   No mycoplasma were detected in the WCB

3) To detect potential exogenous viral contamination of the MCB, samples were [

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----------. All test results on the MCB were negative for adventitious viruses.

Cells from the WCB were examined by ---------- in order to detect structures resembling mycoplasma, fungi, or bacteria that might be contaminating the WCB and unable to grow in standard test media. No adventitious agents were observed

4) Latent viruses: In this study, ---------- ---------- were inoculated with cells from the MCB. [

]. All test results were negative for adventitious virus by these standard methods involving ----------

For the WCB… study was conducted to detect viruses that might be present in a cell line but which do not cause ----------. In this study, ---------- ---------- were inoculated ---------- cells from the WCB. All test results were negative for adventitious virus by these standard methods involving ----------

5) The ------ test was run to determine whether the MCB was contaminated with one or more of ------ adventitious viruses to which hamsters are susceptible (----------). ---------- inoculated with MCB materials were negative for the presence of antibodies to all viruses tested, indicating that none of the viruses were present in the MCB

6) [

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[

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7) In order to evaluate whether infectious retrovirus particles are released by MCB cells---------- ----------. No detectable activity was observed in any culture ---------- assay. The results of these ---------- studies indicate that no retrovirus is being released by the omalizumab-producing cells that is capable of establishing a productive infection in any of the detector cells with which they were ----------

8) Tests of identity were performed to confirm the species of origin of WCB (rhuMAb E25-1A, No. -------) as Chinese hamster. These included ----------. The results of these studies identified the cells as being of Chinese hamster origin

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9) ---------- cell culture production runs using cells from the WCB ----------) were examined for the presence of retroviruses. ---------- of harvested cell culture fluid were collected at the end of each of the cell culture production runs. [

] indicated that up to approximately ---------- retrovirus-like particles per milliliter were present in the harvested cell culture fluid.

For concentration ----- liters of culture fluid from rhuMAb-E25 producing cells was concentrated as per SOP #1220.014 and 1220.008.

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The ---------- lots of harvested cell culture fluid evaluated for retrovirus-like particle numbers were derived from the following South San Francisco qualification campaign cell culture production runs: ----------. These -------- lots were manufactured using the cell culture process described in Section 4.A.2.c.5 of BL103976/0.

Cells and culture fluid from the WCB were collected from a cell culture production run and tested for the presence of retrovirus. At the time of collection, the cells had been in culture for [

] The results of the tests for ---------- retrovirus (---------- however, were negative.

10) The ---------- is performed on cell culture harvests from every production lot. To detect potential exogenous viral contamination, ----------

--------- Potential contamination is assessed for up to --------- by visual observation for ----------. The validity of each test is confirmed by the appropriate positive and negative controls.

All test results on the WCB at the end of production were negative for adventitious viruses.

GENETIC CONSISTENCY (CONSISTENCY OF THE EXPRESSION CONSTRUCT)

In this section we describe the studies performed to demonstrate the genetic consistency of the rhuMAb E25 gene construct in cells used for the production of omalizumab. These studies include nucleotide sequencing of the protein coding region in MCB No. ---------, and restriction digest and copy number analyses of MCB and -------- at the maximum in vitro cell age (WCB No. -------- cultured to -------- days from thaw of the MCB…

Restriction digest analysis was performed to evaluate the organization of the inserted sequence in the MCB and the --------- obtained at ------ days from thaw of the MCB. Genomic DNA prepared from the MCB and ------- was digested with restriction endonucleases (----------). The digestion products were separated by ----------. The digestion pattern produced by the restriction endonucleases was consistent between MCB and ------- No evidence of nucleotide rearrangement, deletion, or insertion within the rhuMAb E25 sequence was detected in the ----- as compared to the MCB cells.

From Study No. GS99-2-1560: rhuMAb-E25 CHO MCB ------- and ------ ------- days in vitro cell age from thaw of the MCB: grown from the WCB ------- in a -- liter pilot production) was used as source of genomic DNA. In addition, cells were grown for --- days, ---------- and then thawed and grown for ---- days in a --- liter pilot production run. Apparently, this lot is produced under non-GMP conditions.

---------- was performed to determine the copy numbers of the rhuMAb E25 gene construct within the MCB and the --------- days in vitro cell age from the MCB thaw). The number of rhuMAb E25 gene copies in the MCB (----------) and in the ----------) was comparable.

---------- was used to generate cDNA from the rhuMAb E25 mRNA expressed in the MCB. The nucleotide sequence of the rhuMAb E25 coding region was determined by ----------. The sequence of the rhuMAb E25 coding region expressed in the MCB was found to be identical to the rhuMAb E25 coding region in the plasmid DNA (----------) that was transfected into the CHO cells used in making the MCB. Upon comparison of these two DNA sequences with the original plasmid sequence (BB-IND -------, Serial No. 000, filed December 20, 1993), single base differences were observed in the rhuMAb E25 ---------- that were attributed to an error in the original sequence analysis of the plasmid. None of these substitutions affected the predicted amino acid sequences.

CONCLUSIONS

The omalizumab-producing cell banks have been confirmed to have an origin consistent with CHO------cells and are free of detectable microbial contaminants. The WCB contains retrovirus-like particles as seen by ----------. The characteristics of these particles are similar to those reported for other retrovirus-like particles from the parental CHO-------- cell line (5,6) and a recombinant CHO cell line (8). ---------- concentrated culture fluids contain detectable reverse transcriptase activity as has been previously reported for other CHO cells (7,8). No infectivity has been detected. Furthermore, the above ---------- study supports a maximum cell age limit for omalizumab production of ---------days since the thaw of the Master Cell Bank.

Genetic consistency in the production of omalizumab has been confirmed for the omalizumab producing cells as recommended in the ICH Harmonized Tripartite Guideline, 30 November 1995, Step 4. The nucleotide sequence in the MCB (No. -------) contains no detectable differences from the sequence in the plasmid (----------) used to transfect the cells. The nucleotide sequence codes for the correct amino acid sequence as confirmed by ---------- No rearrangements, deletions, or insertions within the protein-coding nucleotide sequence were detected in the MCB or in the ---------- days in vitro cell age from MCB thaw). Additionally, the MCB and ------ contain comparable numbers of copies of the rhuMAb E25 gene construct.

Test	Cell bank and ID#
Sterility	----------
Mycoplasma	----------
--------- viral screen	----------
--------- viral screen	----------
------	----------
------	----------
----------	----------

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SUMMARY OF REPRESENTATIVE FULL-SCALE CELL CULTURE RESULTS

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These cell culture performance attributes demonstrate a high degree of consistency in the omalizumab production process.

Attachment 5 Downstream processing: (Downstream)

The omalizumab in the ---------- cell culture fluid (----------) is captured and purified by ----------.

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From CR letter:

We note your commitment from the February-March 2001 inspection that, in future, the polysorbate 20 addition step will be a ----------- process…

From Resubmission (amendment 011):

---------- operations has prepared the equipment and procedures to enable the addition of polysorbate 20 solution in a ---------- manner during the Xolair ----------. The proposed changes to the current procedure include ----------. To improve the capability of this step, additional changes will be implemented to measure the solution quantity ----------. Because no additional Xolair campaigns have occurred since the time of the inspection, the documents for these procedural changes are not yet effective, and the associated equipment is not fully validated. It is our intent to complete these preparations prior to the start of the next ---------- Xolair campaign, and to operate this process step in a manner consistent with our commitment.

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Requirement for Overage

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From Item 4.A.3.a Drug Product Composition

Vial configuration: Nominal 202.5 mg of lyophilized rhuMAb-E25 per vial of finished product. Vial is reconstituted with SWFI (----------) to ----- mL of final formulated product volume at a final concentration of 125 mg rhuMAb-E25 per mL. The pH of the reconstituted product is ----------.
[

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Compendial excipients:

- L-Histidine – USP/Ph.Eur.
- L-Histidine Hydrochloride, Monohydrate – Ph.Eur.
- Polysorbate 20 – NF/Ph.Eur.
- Sucrose – NF/Ph.Eur.
- ----------
- Water for Injection – USP/Ph.Eur.

Manufacturer

Genentech's SSF facility is responsible for aseptic filling, labeling, and packaging operations in the Genentech Parenteral Manufacturing Facility (Building -) and in Building --. DP manufacturing and testing are at SSF and ---. An alternate sterility testing facility is ----------.

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FILLING AND LYOPHILIZATION

Item 4.A.3.d.2 FILLING AND LYOPHILIZATION

Prior to filling, a Quality Assurance/Manufacturing line clearance is performed. Under ----------, the ---------- bulk is transferred, [

Samples for sterility testing of bulk material are taken from initial filled vials to satisfy the requirement in 21 CFR Section 610.12(a).

[

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The entire filling and stoppering operation is performed within the Critical Primary Area (Class ------). The product is filled into 5 cc depyrogenated USP ---------- glass vials. The fill weight target is -------- g per vial, and fill weights are verified throughout the filling process. The vials are partially stoppered with 20 mm gray -------l rubber lyophilization-type stoppers during the filling process. The vials are trayed and transported ---------- to the lyophilizer for the lyophilization process (refer to Section 4.A.3.d.3). The vials are fully stoppered at the end of the lyophilization process when the lyophilizer shelves are lowered. The lyophilizer is then adjusted to ----------, and the vials are unloaded and transferred to the Critical Secondary Area (Class --------) and then to the Capping Area (Room 8119). The vials are capped with ---------- flip-off type caps. Capping takes place in a Controlled Primary ---------- area (Class 10,000) within the Controlled Secondary Capping Room (Class ----------). Capped vials are ---------- in one of the ----------), and are then transferred to the ----------) in Building ---

From amendment 18:

[

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FINAL VIAL INSPECTION

Prior to inspection, a Quality Assurance/Manufacturing line clearance is performed. Filled vials are -------- inspected and samples are removed from the lot for Quality Control release testing and for the QA Acceptance Quality Level (AQL) Inspection and Reserve Sample Program. During the inspection process, vials may undergo interim storage at ---------- in the ----------. After the inspection is complete, vials are then transferred to Materials Control and stored in the Quarantined Unlabeled sections of -------- Room ----------

LABELING, PACKAGING, AND STORAGE PROCEDURES

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4.A.3.d.7 Container/Closure System and Package Integrity

Omalizumab is filled in ---------- 5 cc USP/Ph. Eur. ---------- glass vials, stoppered with ---------- lyophilization stoppers, and sealed with ----------.

4.A.3.d.8 Sterility Testing Methods and Release Criteria

The sterility testing of omalizumab is performed to reveal the presence of viable forms of bacteria, fungi, or yeast in the product. The test utilizes the procedures defined by the current USP. The sterility test is qualified for omalizumab by evaluating bacteriostasis and fungistasis according to the current USP….

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Attachment 7 Shipping and Shipping Validation: (Shipping)

The container/closure system for omalizumab Bulk for Storage manufactured at the ----------facility remains unchanged from that used at the South San Francisco facility, as described below.

Omalizumab Bulk for Storage is [

The ----------is then held at ---------- until it is transferred to the ---------- area where the bulk is ----------. The ---------- is stored at =-20ºC until it is shipped to South San Francisco facility. For transport, the ---------- is transferred to a ----------) equipped with temperature monitoring devices. ---------- and driven to South San Francisco. On arrival at South San Francisco, the --------is again transferred into ----- storage --------- where it is held until needed for the Final Vial filling process.

From amendment 23, DP shipping:

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Attachment 8 Rationale for use: (Rationale)

The allergic cascade is initiated when IgE binds to high affinity FcεRI receptors on the surface of mast cells and basophils and is cross-linked by allergen. This results in the degranulation of these effector cells and the release of histamines, leukotrienes, cytokines and other mediators. These mediators are causally linked to the pathophysiology of asthma and rhinitis, including airway edema, smooth muscle contraction, airway hyper-reactivity, and altered cellular activity associated with the inflammatory process. They also contribute to the signs and symptoms of allergic disease such as bronchoconstriction, mucous production, wheezing, shortness of breath (dyspnea), chest tightness, nasal congestion, sneezing, itchy, runny nose, and itchy, watery eyes.

Omalizumab binds to IgE at the same site as the high-affinity FcεRI receptor thereby reducing the amount of free IgE that is available to bind to the receptor. Treatment with omalizumab also reduces the number of FcεRI receptors on basophils in atopic subjects, and histamine release is reduced in response to allergen challenge in these subjects.

Based on this mode of action, the safety and efficacy of omalizumab was evaluated in human clinical trials as a new therapy for adults, adolescents and children with asthma or seasonal allergic rhinitis.

Attachment 9 Potency: (Potency)

Biological Characterization (from Item 4.A.2.a.3)

Summary

Omalizumab is a specific humanized monoclonal antibody capable of binding to amino acids located on the Fcε3 constant domain of IgE. The complementarity determining regions (CDR) are derived from the parent murine monoclonal antibody (--------) and the constant regions of omalizumab are derived from IgG1. Omalizumab inhibits binding of IgE to its specific high-affinity receptor, FcεRI, on mast cells and basophils and inhibits in vitro allergen-induced histamine release from these cells. Omalizumab binds with high affinity to IgE with apparent Kd of 0.06 to ---------- as determined by ----------

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The omalizumab Reference Material (----------) was extensively characterized (see Section 4.A.2.e). Its activity was assigned a specific activity of --------- Units/mg. ---------- of the qualification lots were determined and ranged ---------- Units/mg omalizumab.

Specificity:

The principal FcεRI binding site on IgE is located on the ----------… All the critical residues are contained in three [

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----------.

However, the binding of IgE to rhuMAb E25 is different from the binding to its receptor because FcεRI can still bind the IgE ----------.

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POTENCY OF PRODUCTION LOTS OF OMALIZUMAB

For determination of potency, omalizumab lots ---------- concentrations where the activity falls within the linear portion of the reference material standard curve. Each lot is tested in three separate assays. The value for each dilution is obtained by interpolation from the reference material standard curve. The mean of these determinations is then multiplied by the reference material activity to obtain the activity of the lot in units.

The receptor-inhibition activities ranged from ---------- Units/mg.

As might have been predicted, the qualification lots from 1999 had ---------- activity than the reference lot (means were ---------- with SD of ----------). Nevertheless, values appear tight and potency of qualification lots is comparable to the reference standard.

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GNE concludes:

The omalizumab recovery process reduced ---------- omalizumab in the ---------- omalizumab in the -------- pool. This is a ---------- levels of at least ---------- -fold. The Protein A and SP Sepharose ---------s ----------. The omalizumab recovery process is robust and reproducible with respect to ---------- clearance

Samples from each ---------- were analyzed by ---------- ---------- to complement the ----------.

GENTAMICIN REMOVAL

Gentamicin is added to the cell culture ---------- cultures (----------) and production cultures (----------) at a concentration of ----- µg/mL.

The levels of gentamicin in omalizumab in-process samples were analyzed quantitatively by a ----------. The linear range of the gentamicin --------- was approximately ---------- ng/mL, but can vary slightly between ----------

[

]

Gentamicin is reduced to below the limit of quantification of the assay by the steps of the omalizumab recovery process.

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RESIDUAL HOST CELL DNA ANALYSIS

A validation study was performed to show that host cell DNA is reproducibly removed by the omalizumab recovery process to acceptable levels. In addition, [ ] show that this step can further reduce DNA.

[

]

Based on the highest DNA level in the ----- and a maximum single dose of ------- mg, the highest dose of DNA per dose of rhuMAb-E25 expected would be ---- ng.

This compares favorably to the WHO recommended maximum dose of 10 ng per dose.

[

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---------- of rhuMAb E25 Using ----------

The data demonstrate that the assay is specific for rhuMAb E25 compared to other Genentech products. The assay is also precise, as demonstrated by [

] The assay is suitably robust for its intended purpose and is stability indicating for samples subjected to [ ]. The results of this validation demonstrate that Test Procedure Q12392 is suitable for determining the identity of rhuMAb E25.

[

]

Identity of rhuMAb E25 by ----------)

The data demonstrate that the assay is specific for rhuMAb E25, ---------- compared to ---------- of other Genentech products. The assay is also precise, as [

] The assay is suitably robust and is stability indicating for samples of rhuMAb E25 subjected to ----------.

The results of this validation demonstrate that Test Procedure Q12391 is suitable for determining the identity of rhuMAb E25.

[

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From Inspection close-out which lists 483 items:

The validated potency assay test procedure was changed in a manner that could diminish the accuracy and precision of the assay.

Genentech has committed to revising the potency assay, Test Procedure Q12385, to the original validated method to include the ---------- and rhuMAb E25 --------- ----------. Genentech has targeted completion of the revision in May 2001.

----------. No further action is required at this time. The official response appears adequate.

From CR:

In your reply of 13 February 2001 to our request of 13 October 2000 to provide an outlier test to the potency assay, you state that no outlier test is used. From Test Procedure Q12385 (effective 1/26/01), step ----------." This statement is inconsistent with USP <111>: "The arbitrary rejection or retention of an apparently aberrant response can be a serious source of bias." Data cannot be discarded without justification. Please delete step -------- as written and consider the institution of a more objective method for outlier testing. Please submit a revised potency assay test procedure (Q12385) that includes ---------- as committed to during the February–March 2001 inspection.

From Resubmission:

These criteria do not apply anymore. As requested in Question 11b, Test Procedure Q12385 has been revised such that the ---------- method of data analysis to quantitate rhuMAb E25 potency has been replaced by the ---------- test. Therefore, Section 5.3.1 has been deleted.

The current method of data analysis to quantitate rhuMAb E25 potency as described in Test Procedure Q12385 ----------; see Attachment 11-1) uses a ----------. Because this method does not test for ----------, ---------- method for ---------- was implemented in the test procedure.

From DR:

Please amend the SOP to clarify what steps will be taken in the event the ----------. Please amend the SOP to include both the ----------.

From Amendment 18 (reply to DR):

We will amend Q12385 to clarify the steps to be taken when the ----------. Section ---- of Q12385 will be amended as shown highlighted in Attachment 6-1. This is very rare, and in such cases, no reportable value is generated for the sample and a QC discrepancy to investigate the assay performance parameters is initiated per SOP 1100.157.

Per our response to part a above, we will amend Q12385 to address steps to be taken when ----------.

The current Test Procedure Q12385 does not set specifications on fiducial (confidence) limits about the estimated potency. The expectation for this type of specification appears historically to have reflected a concern that variability among the replicate potency determinations included in calculating the reportable value should not be excessive. We believe that this underlying concern is addressed in a more direct and interpretable manner by the requirement (Section 7.2 of the test procedure) that the coefficient of variation (CV) among replicate potency determinations not exceed ------ The width of the confidence interval is directly proportional to the standard deviation of the ----------, so that a criterion based on confidence limits appears only to add complexity, without providing any additional information. It seems that framing the requirement in terms of confidence intervals, as in the European Pharmacopoeia may have been done at a time when animal-based bioassays were the norm. Since ethical and practical considerations typically made repetition of such assays prohibitive, evaluating inter-assay variation was not usually possible. The tradition of providing a summary of intra-assay variation in terms of fiducial limits may have arisen as an attempted substitute. Conducting replicate assay determinations, when possible, is always preferable, and allows acceptability to be judged in terms of the (more relevant) inter-assay variability.

[

]

Accuracy, precision, specificity, linearity, and range addressed. Range is from ~0.1 to ~0.8 mg/mL.

----------Content by a ----------)

The data demonstrate that the assay is accurate and precise over the range of ---------- ----------) of the target polysorbate 20 concentration of ------ mg/mL. The assay is also linear within this range, with a correlation coefficient of -------. The overall mean recovery of polysorbate 20 in the assay was 103% as determined by the method of ----------. The relative standard deviation (RSD) values for repeatability and intermediate precision were =---------- ---------- respectively. It is recommended that the same lot of polysorbate 20 used in manufacturing be used for the preparation of the standard curves in this assay for analysis of rhuMAb E25 bulk lots.

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Gentamicin Determination

The level of gentamicin is determined by a ----------
[

]

Assay Sensitivity and Precision
The nominal assay range is automatically calculated by ----------.
Typically, the useful range for the standard curve in the gentamicin assay (defined as between ---------- on the standard curve) is approximately ---------- ng/mL, but can vary slightly between ----------. All samples are assayed in ---------- in place of the specific monoclonal antibody. This control shows that ---------- is mediated by the specific ---------- and not by a non-specific interaction.
Criteria for assay acceptability:
(1) The background in the control ---------- of the maximum response (no gentamicin).
(2) The ----------
(3) The standard curve matches the historical standard curve, using the criteria that the ---------- ----------

[

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Attachment 13 Hold time validation: (Hold time)

Analysis of the in-process hold time steps for omalizumab demonstrated that the following hold times can be used for the manufacturing process with no effect on product quality:
[

]

…the stability of omalizumab was studied in the ---------- under the storage conditions defined in the Validation Protocol VP99-42.

Aliquots of the ---------- from ------ separate omalizumab lots (----------) were stored in ---------- at the times and temperatures outlined in the Validation Protocol, VP99-42.

Initial and final timepoints were analyzed by the assays listed in Table 12. These assays are considered to be stability indicating.
[

]

The results … demonstrate that omalizumab is stable for the hold time parameters defined …. Analysis of the in-process omalizumab pools by all tests showed no significant changes associated with storage for the specified times.

--------stored at ------°C showed a consistent ---------- in pH (--------- pH units).

The reason for the change in ----- is unknown, but it is commonly observed when handling ------- in the laboratory. ---------- was not measured in any of the small scale hold time studies. Absence of ---------- is assured by the following:

[

]

BUFFER STORAGE TIMES

All of the process buffers used in the omalizumab recovery process maintain their --- and ---------- within an acceptable range while stored in ---------- for the times specified in the manufacturing formulae.

[

]

Attachment 14 Viral clearance studies: (Viral clearance)

From Item 4.A.2.d.2.b

VIRUS CLEARANCE EVALUATION

RETROVIRUS REMOVAL AND INACTIVATION BY THE OMALIZUMAB PURIFICATION PROCESS

Summary

The clearance study results demonstrate that during omalizumab purification, [ ] can be expected through a combination of virus inactivation by [ ], and through virus removal achieved by the [ ]

Introduction

Particles with the morphology resembling retroviruses have been observed in CHO cells by Genentech and others. Particles of similar morphology to retroviruses have also been detected in cells derived from the Master Cell Bank (MCB) (----------). Despite extensive efforts to determine whether these particles were infectious, no such activity has been detected (Section 4.A.2.c.4).

To further assure the safety of the omalizumab final product, we have studied the ability of the purification process to clear a model retrovirus. [ ]

[

]

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From CR letter:
Please establish a new reference standard derived from the production method described for the qualification/conformance lots.
From Resubmission:
A new Reference Lot----------, was prepared from --------- ---------- lots produced during the ---------- campaign. The Certificate of Analysis for this new Reference Lot was approved on 7 May 2002.
From DR letter:
Your response to item 2 included the characterization of a new Omalizumab reference standard. Characterization of the new reference standard appears to be limited to those tests described for ---------- --- release and are supplemented with further testing by ---------- Please provide your protocol for establishing a new Omalizumab reference standard. In addition to the tests described above, the protocol should include tests that provide a quantitative assessment of ---------- with appropriate acceptance criteria.
From Amendment 18:
The protocol for establishing the secondary Reference Material Lot ---------- included only ----- testing. Additional assessment of ----------) was performed at the advice of the Analytical Standards Committee, which oversees the Genentech Reference Materials Program (SOP 1100.018).
From review of Amendment 18:
Per Q7a, each batch of secondary reference standard should be periodically requalified in accordance with a written protocol. An amended protocol was faxed to me on June 9, 2003 and will be formally submitted to the BLA.

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Vial configuration ----------) was also used in Clinical study 010E from bulk manufacture (Bulk Lot No. ---------- produced with ---------- and processed per 1997 methods) in 1998. Clinical studies in **bold** are pivotal.

From Item 4.A.1. CMC Summary

1993: This ---------- was used for most Phase I clinical studies and was administered by ---------- and subcutaneous (SC) routes.

1995: The third reference material (----------) was ---------- vial lot prepared from 1995 bulk Drug Substance.

1996: Clinical configuration ---------- mL of bulk Drug Substance, lyophilized and stored at --------. After reconstitution with ----- mL of SWFI, the Drug Product was concentrated approximately ---------- for subcutaneous administration. This configuration was used for ----------, which supplied the ---SC bioavailability study (Q0723g) and US ragweed Phase III seasonal allergic rhinitis study (Study 006). ----------, which was used for many preclinical tests (e.g., reproductive toxicology), was produced by the same method but with the stoppers inserted before the ----------

From table 3 (invest page 20), the final formulation for ---------- rhuMAb-E25 in ---------- sucrose, ------- histidine-------, and --------- polysorbate 20.

1997: To address ---------- concerns, the ---------- The ---------- bulk Drug Substance filled with this bulk included Final Vial lots ----------, which were used in some US-based clinical studies. The PHS/133C production cultures did not give acceptable yields; so additional production runs were performed using a ----------) autoclaved at ----------bulk lots were used to manufacture Final Vial lots to supply most of the pivotal clinical studies… The current reference material (---------- was produced by pooling bulk ----------

Another clinical vial configuration produced from the ---------- production culture was Product Code ----------), which used a -------- mL fill volume and a ---------- vial. This reduced the product overfill and could allow for reconstitution to -----mg/mL omalizumab with either --------- or SWFI. Some preclinical evaluations (e.g., local tolerance) were performed using --------- reconstitution, but ------- reconstitution of the Drug Product has not been employed in any human clinical trials.

1999: Cell culture production changes introduced during this campaign included [

]), the addition of a ---------- feed to the production ---------- and the introduction of a ---------- approximately ---------- after ---------- step was changed from ----------. Detailed studies demonstrated that the material produced by this to-be-marketed process is equivalent to the Phase III materials, thus no bioequivalence studies are required.

---------- Conformance Data

PURPOSE
To demonstrate that the omalizumab Drug Substance and manufacturing process at Genentech's ---------- manufacturing facility is comparable to that from the South San Francisco manufacturing facility.

Genentech's ---------- facility will provide most or all of the Bulk Drug Substance for market introduction.

The results from -------- omalizumab Drug Substance conformance lots manufactured at the ---------- facility compared to Drug Substance lots produced during the 1999 South San Francisco qualification lot campaign demonstrates that the material produced at the ---------- facility is comparable to the material produced at the South San Francisco facility.

The analyses include comparisons of product ----------. Data supporting the analyses include cell culture and recovery process performance attributes, data from Certificate of Analysis (CofA) tests, results from physicochemical and biological characterization analyses, and process impurity profiles. In addition, a ---------- side-by-side stability study supports the comparability analysis of the ---------- and South San Francisco Bulk Drug Substance lots. CofAs for ---------- conformance Drug Substance lots are provided, along with the complete Batch History Record for --------- lot.

ACCEPTANCE CRITERIA
The product and process attributes for the ---------- conformance lots were compared with those same attributes for South San Francisco qualification campaign lots and to data from pilot scale runs as noted above. The ---------- production process will be considered comparable if the following criteria are met:

[

]

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4.C.6.g CONTAINER AND SHIPPING

[

]

4.C.7 Environmental Assessment – ----------
Regarding the application of 21 CFR 25.31(a) to ----------, Genentech notes that the establishment of second approved manufacturing site does not necessarily ---------- As such, application of 21 CFR 25.31(a) is not necessarily inappropriate. However, application of 21 CFR 25.31(c) does present more compelling case for exclusion, and language supporting Genentech 's statement for categorical exclusion under 21 CFR 25.31(c) is provided below.

As specified in regulation at 21 CFR Section 25.15(d), Genentech states that the original Xolair BLA (Reference No.BL 103976/0) qualifies for categorical exclusion from the Environmental Assessment (EA) requirement. Specifically, under 21 CFR Section 25.31(c), any action on an NDA, abbreviated application, application for marketing approval of biologic product, or supplement to these applications is categorically excluded and ordinarily does not require the preparation of n EA or n Environmental Impact Statement for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

Attachment 17 Stability determining assays: (Stability assays)

From Item 4.A.2.h Drug Substance Stability

The omalizumab Drug Substance qualification lots are being tested according to the protocol summarized in the following table:
[

]

Amendment 16 provided data in support of DS stability out to --- months.

Stability of drug product Lots are tested according to the following table:

[

]

The stability protocol for drug product Lots to be placed in the stability program annually will only include all validated tests above with the exception of Q12024 ----------

From CR letter:

Comprehensive assessment of Omalizumab ---------- (e.g., by ---------- of Omalizumab) is not routinely performed…

Please incorporate an assay that can comprehensively measure Omalizumab ---------- for:

- the establishment of new reference material
- lot release; and
- stability studies.

From Resubmission:

A ---------- method has been developed and validated as Test Procedure Q12435 (---------- rhuMAb E25).

Attachment 18 Stability data supporting dating period: (Stability dating**)**

From Item 4.A.2.h - Drug Substance Stability

The data were generated from Lot ----------, which was manufactured in 1997, and from Lots ----------, which were manufactured during the 1999 campaign. The studies have been performed at the recommended -------- storage conditions of -----C as well as at the ---------- storage condition of 2-8ºC. The results from these studies demonstrate the following:

Lot ---------- remained well within all stability specifications after ---months storage at ---------. No significant changes were observed.

---------- remained well within all stability specifications after -- -------- storage at 2-8ºC and after -- months storage at ---ºC in ----------. No significant changes were observed for either storage condition.

No significant differences in the stability profile were observed between Lots ---------- ---------- after -- months storage at ---ºC, indicating that the Drug Substance materials produced during the ------ different ---------- L scale campaigns are comparable.

Undergoing three ---------- does not impact the quality of omalizumab Drug Substance.

The data support --month expiry dating at 2-8ºC and --- months at ---ºC with up to ---------- -------- for omalizumab Drug Substance.

Amendment 16 provided data in support of DS stability out to --- months.

4.A.3.f Drug Product Stability

The data presented in this report support the proposed expiration dating of --- months at 2-8ºCfor the lyophilized product. Additional real-time stability data to support the proposed expiration dating will be provided in a stability update.

The intended ***{Trade Name}*** market configuration, ---------- contains 202.5 mg of omalizumab lyophilized powder in a single-dose, 5 cc vial (----------Type I glass) sealed with ---------- mm stoppers. Each vial is filled with 5.0 mL omalizumab at 40.5 mg/mL in 85 mM sucrose, 5 mM histidine, 0.01% polysorbate 20, pH 5.7 6.4. After reconstitution with 1.3 mL Sterile Water for Injection (SWFI), USP, the vial delivers 150 mg of ***{Trade Name}***.

Note: The fill weight target is ---------- g per vial which implies a density ------.

Stability data were generated from the following Lots:

[

]

In addition, stability data from two other product codes (Code ----------, 5 cc vial configuration, 150 mg dose and ---------- configuration, 150 mg dose) are presented.

All vial configurations were produced using the same Bulk for Storage formulation, containing 40.5 mg/mL omalizumab, 85 mM sucrose, 5 mM histidine, 0.01% polysorbate 20, at pH 6.1.

Lots ---------- met all stability specifications up to --- months storage at 2°C 8ºC and after -- months storage at ---C. No significant changes were observed for either storage condition

Qualification lot data only goes out to -- months. By proposed licensing date (----------), qualification lot data will be at ---------- months.

---------- vial real time stability provided in amendment ---------- months support a claim for ---- month stability.

Photostability:
[

]

The effect of light exposure on ***{Trade Name}*** Drug Product was evaluated by comparing the analytical results for light exposed samples with the control ----------). Table 12 summarizes the results obtained from the photostability study of Lot ----------. No changes were observed in ----------
. All samples met stability specifications.

Apparently only assessed the lyophilized, not reconstituted product. Reconstituted product photostability data were submitted via e-mail on June 12, 2003 but did not include ------

STABILITY OF *{Trade Name}* DRUG PRODUCT AFTER RECONSTITUTION
Vials of ---------- were reconstituted and stored at either ----------..

After storage of the reconstituted Drug Product Lot ---------- at 2°C 8C for --- hours and ------ for ----------, the samples were assessed by ---------- and compared against the control (----------). No significant differences were observed in the data between the control, the vial held at 2°C 8C for --- hours, and the vial held at ---C for up to --- hours and the samples met all stability specifications.

SHIPPING AND HANDLING OF *{Trade Name}* DRUG PRODUCT

Studies to support the shipping and handling of ***{Trade Name}*** will be presented in the Drug Product stability update.

Note that the stability protocol presented at inspection differs from that presented at the pre-BLA meeting and from that presented in the BLA. Specifically, ---------- at -- months is removed in the protocol presented at inspection ---------- analysis is removed from protocol presented in the BLA. The frequency of testing has been reduced in the BLA versus pre-BLA (BLA consistent with Q5c). Protocol was subsequently amended to be compliant with ICH guidelines.

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Attachment 20 Release tests and specifications for the final product: (Final product specifications)

From Item 4.A.3.b Specifications and Methods of Drug Product Ingredients

Compendial Excipients:
L-Histidine - USP/Ph. Eur.
L-Histidine Hydrochloride, Monohydrate - Ph. Eur.
Polysorbate 20 - NF/Ph. Eur.
Sucrose - NF/Ph. Eur.

Water for Injection - USP/Ph. Eur.

[

]

No non-compendial excipients are used in the manufacture of rhuMAb-E25.

4.A.3.e Specifications and Analytical Methods for Drug Product

The sterility of the ---------- Bulk is verified by performance of a sterility test using either samples obtained from the ---------- or from samples ----------

A subset of purity and molecular consistency assays are performed on Final Vial based on their ability to detect changes during lyophilization and storage of Drug Product.

[

]

Data from final vial Lots ---------- are presented and fall within the specifications listed.

QUALITY [

].

QUALITY [

]

IDENTITY ---------- (Q12391)

Each molecule produced at Genentech has a unique ----------, allowing the discrimination of omalizumab from other Genentech produced molecules.

Using Test Procedure Q12391, positive identity is confirmed if [

.] Results obtained from ----- Final Vial lots were used to establish the specification; all lots met the positive identity criterion.

PURITY ----------

The release specification was derived from data obtained from ------ qualification lots. The results from these qualification lots and clinical lots (----------) support the specification. The proposed specification for the product at the end of shelf life is ----------. This allows for a ---% decrease of the ----------, which is supported by the stability studies performed to establish the product dating and stability during shipping and handling.

PURITY ----------

…specifications limits were established on the amounts of ---------- The specification limit on --------- is supported by the acceptable potency observed (----------Units/mg) for an omalizumab accelerated degradation sample containing ----------

The range of the --------- content observed in ---------- Bulk for Storage lots ---------- The ranges of ---------- in these lots were ---------- respectively.

PURITY ----------

… specification is based on the minimal ---------- response concentration and the sensitivity of the assay. A specification of less than or equal to ---------- corresponds to ------- ---------- of omalizumab. At a maximum omalizumab dose of --------- mg/kg, a Final Vial lot released at the specification limit of ---------- would have a ---------- of approximately --------- compared to the minimal ---------- response concentration of ----------
All lots tested showed results below the proposed specification

POTENCY ----------

…validation studies demonstrated an overall accuracy of ---------- recovery studies. The assay was precise with an overall relative standard deviation of ---% (see Section 4.A.7, Test Methods Validation). Based upon these studies, the standard assay format was set at ----------

The results from ---------- L scale lots ranged from ---------- Units/mg.

STRENGTH ----------

This procedure is employed as a measure of the protein content in omalizumab Final Vials. Omalizumab Drug Substance is produced at a concentration of ----------, and filled based on a fill weight targeting a Final Vial content of 202.5 mg/vial. The fill weight is strictly controlled for

by operational procedures and lower/upper tolerance limits. This procedure combined with the action limit on the bulk protein concentration prior to fill ensures consistent Final Vial content. The results of --------- Final Vial lots ranged from ---------- mg/vial. These results justify the proposed specification.

EXCIPIENT/CHEMICAL COMPOSITION ----------)
The ----------measurement is employed as a verification of the total content of sucrose and histidine in the formulation of omalizumab Final Vials. This test, in combination with the pH determination, ensures the correct composition (except for polysorbate 20) of omalizumab Final Vials. The specification for ----------of the Final Vials was established from results obtained from ---------- omalizumab Final Vial lots, and was supported by the theoretical value for the composition of the product. The results from these lots were between ---------- mmol/kg. These data, in addition to supportive stability data from development experience, justify the specification.

EXCIPIENT/CHEMICAL COMPOSITION pH DETERMINATION (Q12003)
The results from t------ omalizumab Final Vial lots were at ----------. These results, in addition to supportive data demonstrating the stability of omalizumab at the specification limits, justify a specification of pH ---------- after reconstitution.

EXCIPIENT/CHEMICAL COMPOSITION MOISTURE DETERMINATION (Q12024)
This test is performed as a measure of residual moisture content of the product cake after lyophilization. Residual moisture data from ------ omalizumab qualification lots ranged from ----- These data, in addition to supportive data demonstrating the stability of omalizumab at the specification limit, justify a specification of ------- moisture in the Final Vial.

SAFETY STERILITY TEST (Q12002)
Data from all ------ lots met the current specification of ----------

From CR letter:

Comprehensive assessment of Omalizumab ---------- (e.g.----------) is not routinely performed… Please incorporate an assay that can comprehensively measure Omalizumab ---------- for lot release.

From reply to DR: Drug Product Release: ----------

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Attachment 23 Referenced master files: (Master files)
{for diluents, container and closures, etc}

In Item 4, volume 4 of 7 on page 97 (product) is a letter from ----------
authorizing Genentech to reference ---------- relating to ----------.

In Item 4, volume 4 of 7 on page 98 (product) is a letter from ----------
authorizing Genentech to reference DMF number ------ which describes ----------
---