DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Date: May 30, 2007

To: File STN 125202, 125203, 125204, 125205, 125206, 125207, 125208, 125212, 125213, 125214, 125215, 125216, 125217, 125218, 125219, 125220, 125221, 125222, 125223, 125224, 125225, 125226, 125228, 125229, 125230, 125231, 125232, 125233, 125242

From: George R. Gentile, Senior Regulatory Review Officer, CBER/OCBQ/DMPQ/MRBII, HFM-676

Through: Chiang Syin, Ph.D. Chief, DMPQ, MRB II, HFM-676

Subject: Review Memorandum – Biotest AG, license number 1702. Original Application / Prior Approval Supplement Received on September 22, 2006 with an Action Due Date of July 30, 2007.

Type

Original Application / Prior Approval Supplement for the following (see Short Summaries):

Products

Anti-E (Monoclonal) (Formulated for Automated Testing)
Anti-e (Monoclonal) (Formulated for Automated Testing)
Anti-K (Monoclonal) (Formulated for Automated Testing)
Anti-c (Monoclonal) (Formulated for Automated Testing)
Anti-C (Monoclonal) (Formulated for Automated Testing)
Reagent Red Blood Cells
Reagent Red Blood Cells For use in Automated Systems
Anti-Fya (Monoclonal)
Anti-P1 Monoclonal)
Anti-s (Monoclonal)
Anti-Human Globulin
Anti-S (Monoclonal)
Anti-Jkb (Monoclonal)
Anti-D (Monoclonal) (IgG Blend) Formulated for Automated Systems
Anti-A (Murine Monoclonal)
Anti-B (Murine Monoclonal)
Anti-A,B (Murine Monoclonal)
Anti-D (Monoclonal) (IgM)

File STN Multiple

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Anti-D (Monoclonal Blend)
Anti-M (Murine Monoclonal)
Anti-N (Murine Monoclonal)
Anti-C (Monoclonal)
Anti-E (Monolocnal)
Anti-e (Monolocnal)
Anti-K (Monolocnal)
Anti-Jka (Monoclonal)
Anti-k (Murine Monoclonal)
Anti-Lea (Murine Monoclonal)
Anti-Human Globulin (Rabbit/Murine Monoclonal)

Short Summaries

- Anti-E from the cell lines MS260/MS12 intended for use on the Erytype S Rh+K Type plate for Rh subtyping and Kell Typing
- Anti-e from the cell lines MS16/MS21/MS63 intended for use on the Erytype S Rh+K Type plate for Rh subtyping and Kell Typing
- Anti-K from the cell line MS56 intended for use on the Erytype S Rh+K Type plate for Rh subtyping and Kell Typing
- Anti-c from the cell line MS33 intended for use on the Erytype S Rh+K Type plate for Rh subtyping and Kell Typing
- Anti-C from the cell lines MS24/P3x25513G8 intended for use on the Erytype S Rh+K Type plate for Rh subtyping and Kell Typing
- Licensure of Biotestcell A1,B and Biotestcell A2 for reverse grouping in tube testing and the Biotestcell Pool, Biotestcell 1,2, Biotestcell 3 for the detection of unexpected antibodies in the tube test, and Biotescell I8 and Biotestcell I11 for the exact identification of unexpected antibodies in the tube test
- Licensure of Erytypecell A1,B, Biotestcell Pool, Biotestcell 1,2 , Biotestcell 3, Biotestcell I8 and Biotestcell I11 for use on the TANGO
- Licensure of Seraclone Anti-Fya (clone DG-FYA-02) for use in manual tube agglutination method
- Licensure of Seraclone Anti-P1 (clone 650) for use in manual tube agglutination
- Licensure of Seraclone Anti-s (clone P3YAN3) for use in manual tube agglutination method
- BLA for Anti-Human Globulin (Rabbit) (for tube test)
- Licensure of Seraclone Anti-S (Monoclonal), clone MS 94 for use in manual tube agglutination method
- Licensure of Seraclone Anti-Jkb (Monoclonal), clone MS 8, for use in manual tube agglutination method
- Licensure of Anti-D (Monoclonal) (IgG Blend) from clones BS221/H41 11B7 for use with the TANGO Automated Blood Bank System and Solidscreen II plates
- Licensure of Seraclone Anti-A (Murine Monoclonal), clone A003, for use in manual tube agglutination methods
- Licensure of Seraclone Anti-B (Murine Monoclonal), clone B005, for use in manual tube agglutination methods

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- Licensure of Seraclone Anti-A,B (Murine Monoclonal), clones BS63 and BS85, for use in manual tube agglutination methods
- Licensure of Seraclone Anti-D (Monoclonal) (IgM), clone BS226, for use in manual tube agglutination methods
- Licensure of Seraclone Anti-D (Monoclonal Blend), clones BS232, BS221 and H4111B7 for use in manual tube agglutination methods
- Licensure of Anti-M (Murine Monoclonal), clone BS57, for use in manual agglutination methods
- Licensure of Anti-N (Murine Monoclonal), Clone BS41, for use in manual agglutination methods
- Licensure of Anti-C (Monoclonal), clone MS24, for use in manual agglutination methods
- Licensure of Anti-E (Monolocnal), clones MS12 and MS260, for use in manual agglutination methods
- Licensure of Anti-e (Monolocnal), clones MS16, MS21 and MS63, for use in manual agglutination methods
- Licensure of Anti-K (Monolocnal), clone MS56, for use in manual agglutination methods
- Licensure of Anti-Jka (Monoclonal), clone MS15
- Licensure of Anti-k (Murine Monoclonal), clone Lk1
- Licensure of Anti-Lea (Murine Monoclonal), clone LeA2
- Manufacture of Anti-Human Globulin, Anti-IgG + Anti-C3d (for tube test)

Action Recommendation

A Complete Response (CR) letter conveying the review issues should be sent to the sponsor.

Background

All of the *in vitro* product facility information in the BLA Establishment Description sections is the same for the Blood Grouping Reagents (BGR) and Anti-Human Globulin (AHG). The Blood Grouping Reagents include all of the *in vitro* products manufactured from *in vitro* substances purchased from Celliance, Diagast, [redacted]. The facility review includes the water system, HVAC system, compressed air system, computer systems, contamination/cross contamination issues, environmental monitoring and process validation.

[redacted]

Blood Grouping Reagents (BGR) CMC Summary

The Seraclone Blood Grouping Reagents are produced from blends or individual monoclonal antibodies (*in vitro* substances) provided by several manufacturers under contract manufacturing or shared manufacturing arrangements. The optimal dilution of the antibodies is determined by Biotest in small scale pilot lots. The optimal formula is then used to produce marketed product.

Preservative (0.1% sodium azide) and varied, product specific diluents and colorants (if needed) are added to each antibody pool, [redacted] The [redacted] bulk products are sublotted [redacted] prior to vial filling. The antibodies are then automatically filled into 5mL or 10mL glass vials, with pipette top screw cap closures. The vials are overfilled to assure a fill volume of at least 2 mL, 5 mL or 10mL per vial.

The products are tested for potency and specificity to assure that all in-process and final product specifications are met. All testing uses [redacted] methods. A reference standard is run in the assays for comparison purposes. Use of a reference standard during release testing assures that the test results are reliable and that the products consistently meet established specifications.

The final product is sampled, and Quality Control tested for potency and specificity before packaging. The QC testing data of final product from each sublot bottle is trended and reviewed to ensure that all sublot bottles are equivalent.

BGR Manufacturing Process Flow

[redacted]

Anti-Human Globulin (AHG) CMC Summary

Serum is collected from rabbits that have been immunized with purified human IgG. [redacted]

The *in vitro* products are formulated and mixed with the specified components, colorants and 0.1% sodium azide (preservative). Other components are then added such as [redacted]

Vials are filled with 10mL of product, and closed with a pipette top closure. The vials are overfilled to assure a fill volume of at least 10mL in the 10 mL vials. Fill volume checks are performed throughout the fill. Individual vials are labeled, placed into final packaging cartons, the cartons labeled, and the final product is then stored at 2-8°C. The AHG reagents are packaged in kits of 10 vials per kit.

The potency and specificity are tested on the final product and on in-process samples during the manufacturing process. All testing uses [redacted] A reference standard is run in the assays for comparison purposes. Use of a reference standard during release testing assures that the test results are reliable and that the Anti-Human Globulin, Anti-IgG and the Anti-Human Globulin, Anti-IgG + Anti-C3d products consistently meet established specifications.

Final product is sampled, and Quality Control tested for potency and specificity before packaging. The QC testing data of final product from each sublot bottle is trended and reviewed to ensure that all sublot bottles are equivalent.

AHG Manufacturing Process Flow

[redacted]

Reagent Red Blood Cells (RRBC) CMC Summary

in-vitro product Reagent Red Blood Cells are prepared from the [redacted] suspended in Alsever's solution that contains preservatives. Alsever's solution with [redacted] is used for Biotestcell A_1B, Erytypecell A_1B, and Biotestcell A_2 only. The remaining Biotestcell products use Alsever's solution [redacted] The red cells are then mixed with Alsever's solution to a final concentration of either [redacted] or 3.0-3.4% depending on the product.

The final product is filled into glass vials, either [redacted] or 10mL per vial, with pipette tops that are automatically applied and tightened. The vials are labeled, and placed into cartons. The expiration dating period is 56 days at 2-8ºC.

The RRBCs are tested in-process for [redacted] to assure that all specifications are met. Final product positive and negative specificity testing is performed to verify that no mix-ups have occurred and to validate the formulation and filling.

RRBC Manufacturing Process Flow

Pages 7 through 20 redacted for the following reasons:
- -
determined to be not releasable

[redacted]

[redacted]

Internal Comments

1. Copies of the proposed (draft) labels for the Seraclone® Blood Grouping Reagents, vials, cartons, and the respective (draft) Package Inserts should be reviewed.
2. Copies of the proposed (draft) labels for the Reagent Red Blood Cells, vials, cartons, and the respective (draft) Package Inserts should be reviewed.
3. Copies of the proposed (draft) labels for the Anti-Human Globulin vials, cartons and the respective (draft) Package Inserts should be reviewed.
4. Product review should be completed.
5. The Organization of the submission was poorly grouped. The submission should have been separated into three groups: Blood Grouping Reagents (BGR), Anti-Human Globulin (AHG) and Reagent Red Blood Cells.
6. All of the *in vitro* product facility information in the BLA Establishment Description sections is the same for the Blood Grouping Reagents (BGR) and Anti-Human Globulin (AHG). The Blood Grouping Reagents include all of the *in vitro* products manufactured from *in vitro* substances purchased from Celliance, Diagast, [redacted]
7. [redacted]

8. There are multiple documents that are not translated to English. These were noted by the product reviewer.
9. Sterilization validation data and reports should have been provided in the submission instead of referenced. These data and reports should be reviewed during inspection.

Comments for Manufacturer

1. Please define and specify the range of room temperature in the Standard Operating Procedures. Reference is only made to "RT".
2. The Description of the Container Closure system states that the potency data provides evidence that there are no adverse effects, nor interfering substances that leech out of the container/stopper system during the prolonged storage interval. Please provide an explanation [redacted]
3. The submission includes transport stability data that was simulated. Biotest AG should design and perform a shipping study that validates the transport of the product from the manufacturing facility in Germany to the United States end-user.
4. Please provide your process for revalidation to establish ongoing evidence that all specific processes will consistently produce a product meeting its pre-determined specifications and quality characteristics.
5. Please provide your process for Continuous Environmental Monitoring to demonstrate that environmental quality is consistently within specified levels.
6. Operational Qualifications were not submitted with the [redacted]
7. An additional package integrity/stability testing on [redacted] is currently in progress. Biotest AG should submit the data/results at the completion of the study.
8. An additional study on [redacted] is currently in progress for package integrity and stability. Biotest AG should submit the data/results at the completion of the study.

End Memorandum

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