



MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: December 19, 2006

To: Files of STNs 125216/0 and 125217/0
/S/

From: Teresita C. Mercado, Consumer Safety Officer, Devices Review Branch

Subject: Review memo: Biotest AG's Blood Grouping Reagents Anti-S (Monoclonal) and Anti-Jk^b (Monoclonal)

Through: Sheryl A. Kochman, Chief, Devices Review Branch /S/

Background:

Biotest AG, located in Dreieich, Germany submitted these applications for the manufacture of Seraclone[®] Blood Grouping Reagents (BGR) Anti-S (Monoclonal) and Anti-Jk^b (Monoclonal) which are intended for typing blood specimens using manual tube agglutination methods. Seraclone[®] Blood Grouping Reagents have been distributed worldwide since 1997.

Regulatory documents in the submission include Form FDA 356h, draft labeling, chemistry, manufacturing and controls, establishment information, stability data, and batch records (Anti-S, lot 1150805 and Anti-Jk^b, lot 1111299).

Also included in the submission is the protocol for stability testing under container closure conditions.

Review:

Manufacturing Summary

The Anti-Jk^b (For Further Manufacturing Use) and Anti-S (For Further Manufacturing Use) materials are supplied by Celliance Ltd. under a shared manufacturing agreement with Biotest AG.

The following table shows the cell line and antibody type of the products that are the subject of this memorandum.

Product	Clone	Antibody Type	Volume per vial x vials per kit	Preservative	Shelf Life
Seraclone [®] Anti-S	MS 94	Human/Mouse IgM	2 ml x 1	0.1% NaN ₃	18 months
Seraclone [®] Anti-Jk ^b	MS 8	Human/Mouse IgM	2 ml x 1	0.1% NaN ₃	20 months



Field Trials

Field trials were conducted at five (5) sites that included University of Virginia in Charlottesville, VA, Heartland Blood Center in Aurora, IL, University of Colorado Medical Center in Denver CO, Wake Forest Baptist Medical Center in Winston-Salem, NC and Olympus America, Inc. Laboratory in Irving TX. Samples were collected from both normal blood donors and patients at the test sites except for the OAI testing facility where samples were obtained from normal samples from the Gulf Coast Blood Center.

The table below summarizes the rate of agreement for the Anti-S (Monoclonal) and Anti-Jk^b (Monoclonal) and the reference method(s).

Trial Reagent	Number in Agreement	Number of tests	% Agreement	Lower 95% Confidence Limit
Anti-S (MS 94)	230	230	100%	98.7%
Anti-Jk ^b (MS 8)	259	259	100%	98.9%

Review Questions:

Questions and Comments are written to address the sponsor directly.

1. Conformance lots for Anti-S and Anti-Jk^b. Please note that we will inform you when to submit the test data, lot release samples, and protocols for the three conformance lots in support of these BLAs. We recommend that you manufacture at least three (3) conformance lots per product. We will accept two (2) pilot lots and one (1) full conformance lot per product. Please submit the batch records of the full-scale conformance lot for each product. This information will be communicated to you by telephone at the appropriate time.
2. Volume I, Summary, page 4 of 11. This section states, “The [REDACTED] bulk products are sublotted [REDACTED] prior to vial filling.” Also, “The QC testing data of final product from each sublot bottle is tended and reviewed to ensure that all sublot bottles are equivalent.” Please describe how you perform sublotting of your products, including a description of the tests and their specifications to verify that each sublot is identical and equivalent to the other sublots of the lot. Please refer to 21 CFR 660.21(a)(4) for labeling identification of sublots.
3. Title 21 CFR 610.14 requires that the contents of a final container of each filling be tested for identity after all labeling operations have been completed. The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars and distinguish it from any other product being processed in the same laboratory. Please submit the list of identity tests that you perform for each product.
4. Volume I, Summary, Sensitivity/Specificity, page 9 of 11. Please clarify if you performed a separate study using a gold standard method to determine the sensitivity and specificity of your reagents. If not, please be advised that results of calculations derived from comparison testing with another “imperfect test method” should be described as positive and negative agreements.
5. Please clarify if each of the lots used in the filed trials was produced from a separate batch of antibody, beginning at the stage of thawing frozen aliquots of the working cell bank as recommended in the March 1992 draft guidance, *Points to Consider in the Manufacture of In Vitro Monoclonal Antibody Products for Further Manufacturing Into Blood Grouping Reagent and anti-Human Globulin*.
6. Please submit the data that demonstrate the lot-to-lot consistency of each one of the Blood Grouping Reagents. We recommend that you perform a lot-to-lot variability study using at least three (3) lots per reagent. You should obtain data for at least three (3) lots; each of the three lots should have been produced from a separate batch of antibody, beginning at the stage of thawing frozen aliquots of the working cell bank.

7. Volume I, Draft Labeling, Vial Label.

- a) Please clarify what the “ACT” on the vial label stands for. “ACT” is not included in the Glossary of Symbols. Moreover, since it is not listed in the guidance, *Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use*, it has to have an English translation on every label (other than the Package Insert [PI]) it appears.
- b) The symbol you use for preservative is the word PRES in a box. Since it is not listed in the guidance, *Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use*, it has to have an English translation on every label (other than the PI) it appears.
- c) Please replace “FDA Lic.” With “U.S. Lic.”

Volume I,”

8. Volume I, Draft Labeling, Carton Label.

- a) Please replace “FDA Lic.” With “U.S. Lic.”
- b) The symbol you use for preservative is the word PRES in a box. Since it is not listed in the guidance, *Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use*, it has to have an English translation on every label (other than the PI) it appears.

9. Volume, I, Package Inserts, Anti-Jk^a and Anti-Jk^b and Anti-S.

- a) Please replace “FDA License” With “U.S. License.”
- b) For clarity, please replace the word “characteristics” under the Intended Use section with the word “antigen”. The statement should read, “For the determination of the _____ antigen of red blood cells using the tube test.
- c) The Summary section of the Anti-Jk^a package insert consists of the following statement: “The Kidd antigen was first identified in 1951 when the corresponding antibody was found to cause hemolytic disease of the fetus and the newborn (HDFN). Although Kidd antibodies have been shown to cause generally mild HDFN, they have been implicated in severe transfusion reactions (HTR). The HTR are often delayed due to an anamnestic response to the Kidd antigen.¹” Title 21 CFR, section 809.10 (b)(3) states that the Summary Section (Summary and explanation of the test) must include a short history of the methodology, with pertinent references and a balanced statement of the special merits and limitations of this method or product. The statement in your package insert does not

address this requirement. Please revise the Summary section by adding the required information per 21 CFR section 809.10 (b)(3).

- d) The Summary section of the Anti-S package insert consists of the following statement: “Antibodies to the S antigen usually occur following immunization and are capable of causing hemolytic disease of the fetus and the newborn (HDFN) and hemolytic transfusion reactions (HTR).¹” Title 21 CFR, section 809.10 (b)(3) states that the Summary Section (Summary and explanation of the test) must include a short history of the methodology, with pertinent references and a balanced statement of the special merits and limitations of this method or product. The statement in your package insert does not address this requirement. Please revise the Summary section y adding the required information per 21 CFR section 809.10 (b)(3).
- e) According to the Specimen collection section, fresh samples of clotted, EDTA or citrate anticoagulated whole blood collected following general blood sampling guidelines are acceptable. However, according to page 20 of the December 2005 Investigational Plan, both patient and donor samples used in the testing will be collected in EDTA. Please submit the data from a study or studies that support the use of the various samples that are acceptable for testing with your reagents as indicated in the labeling. This study should also support the acceptable sample age and storage conditions as stated in the labeling. Please note that samples commonly used in the U.S. include those collected in EDTA, heparin, ACD, CPD, CPDA-1, CP2D and samples without anticoagulant.
- f) Under “Materials required but not provided”, please specify the dimensions of the tubes that should be used.
- g) Under “Note”, please replace the statement “Manage waste according to national guidelines” with “Manage waste according to local, state and national regulations”.
- h) Glossary of Symbols. Please include “ACT” and its definition under in the table. Moreover, since it is not listed in the guidance, *Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use*, it has to have an English translation on every label (other than the PI) it appears.

i)



Volume I, Package Insert, Anti-S.

- k) Limitation Section. Please include a statement regarding false negative or weakened reactivity if red blood cells are inadvertently exposed to bleach or bleach-containing products.
10. Volume I, Investigational Plans, December 2005, Figures 3, 4 and 5, pages 9, 10 and 12. Your criteria for investigating “no type determined” (NTD) does not appear to include the investigation of the cause of the initial NTD if the retest results are concordant. CBER believes that in order to better understand the performance of your reagent, it is important to investigate all NTD and discrepant results including those that are concordant upon retesting. The same rationale can be applied to the red cell typing or antibody identification that had initial discrepant results but were concordant after retesting. Please comment.
11. Volume I, Investigational Plans, Statistical Analysis, page 22. According to the test protocol, “The rate of agreement will be recalculated after repeat testing, discrepancy resolution, and exclusion of samples associated with a limitation of the reagent or that did not give an interpretation (i.e., due to sample condition or flagged as invalid). This rate of agreement will be compared to the expected results for that sample rather than the reference method.” Since the new test method is being compared to a reference method, the rate of agreement should be based on agreement with the reference method and not the expected results of the sample. You should explain how discrepant results were resolved by a referee method but should not include these in the calculation of the rate of agreement.
12. Volume I, Investigational Plans, Sensitivity and Specificity for TANGO test components, page 23. The reagents you are seeking licensure for are used for manual techniques. Please explain why the Investigational Plan includes TANGO test components.
13. Volume I, Investigational Plans, Records, pages 26 - 28. The Investigational Plan states that the IRB, investigator and sponsor must maintain records for a period of two years after the completion or termination of the investigation. 21 CFR 56.115 (b) requires that records and reports be retained for at least 3 years after completion of the research and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner. Please comment.
14. Volume I, Investigational Plans, Attachment A, IRB Waiver Letter, page 29 and Attachment B, Investigator Agreement, page 30. There is no Attachment A or

Attachment B in the submission. Please clarify and submit the documents as necessary.

15. Volume I, Clinical Data Sections, page 8. There were only two (2) sites, i.e., University of Virginia and OAI, which performed testing on the rare antisera. Thirty samples (30) were tested at the University of Virginia and 991 samples were tested at the OAI. Please explain your rationale for the limited testing performed on the rare antisera. CBER requires field trial testing in at least one other site.
16. Volume I, Clinical Data Sections, page 29. Please explain, “Note: The reference methods for the antibody screen are listed in Table I.e. The field trial sites did not match their reference reagents to the trial reagents.”
17. Volume II, Chemistry, Manufacturing and Control Section, Description of the *In Vitro* Product, page 6 and Testing Methods and Acceptance Criteria, page 21. The potency titer specification for the Seraclone Anti-Jk^b is [REDACTED] Although title 21 CFR 660.25 requires a minimum potency of 2+ reaction with undiluted reagent, because of stability concerns, we recommend a minimum potency of 1:8 for monoclonal antibodies as described in *Recommended Methods for Blood Grouping Reagents Evaluation*, Docket No. 84S-0181, dated March 1992.
18. Volume II, Chemistry, Manufacturing and Control Section, page 29. This section states, “The Blood Grouping Reagents are tested for specificity and potency using [REDACTED] [REDACTED] These methods are well established and widely accepted standard methods for blood grouping analysis, therefore they do not require method validation.” Please note that although these methods are widely used and published, you are required to show that your staff is capable of performing these methods and obtaining correct results consistently in your facility. Please provide evidence that your staff can perform these methods correctly and consistently, i.e., that results are reproducible from one technologist to another.
19. Volume II, Chemistry, Manufacturing and Control Section, Appendix 7, SOP-DS;Q-3036-04/03, Test Specification serological final control of Seraclone[®] Anti-Jk^b (JK2) in-vitro diagnosticum.
 - a) Please explain how you arrived at your decision for you choosing a [REDACTED] in some of your serological testing.
 - b) As described in The *Recommended Methods for Blood Grouping Reagents Evaluation*, “To confirm the absence of contaminating antibodies, each lot of Blood Grouping Reagent should be tested and interpreted by the most sensitive method(s) described in the manufacturer’s package insert. Maximum parameters (drops of reagent, incubation time, centrifugation, etc.)

should be followed.” The package insert recommends [REDACTED]

[REDACTED]

20. Volume II, Chemistry, Manufacturing and Control Section, Appendix 7, SOP-DS:Q-3042-04/02, Test Specification serological final control of Seraclone[®] Anti-S (MNS3) in-vitro diagnosticum.

c) Please explain how you arrived at your decision for you choosing a [REDACTED] in some of your serological tests.

a) As described in The *Recommended Methods for Blood Grouping Reagents Evaluation*, “To confirm the absence of contaminating antibodies, each lot of Blood Grouping Reagent should be tested and interpreted by the most sensitive method(s) described in the manufacturer’s package insert. Maximum parameters (drops of reagent, incubation time, centrifugation, etc.) should be followed.” The package insert recommends [REDACTED]

[REDACTED]

21. Volume II, Chemistry, Manufacturing and Control Section, Appendix 9. Some of the documents included in this attachment are written in German. To facilitate the review, please submit the English translations of these documents.

22. Volume II, Chemistry, Manufacturing and Control Section, Appendix 10, DOOQF-003, Stability testing for the blood group reagents under container closure conditions, page 4. One of the acceptance criteria for this study is that the reagents may not escape during storage. Please explain how you determine that no reagent has escaped during transport, and storage throughout the shelf life of the products.

23. Volume II, Chemistry, Manufacturing and Control Section, Appendix 13, SV-DS:Q-0100-00/10. The document in this appendix is written in German. Please provide an English translation of the document.

24. Volume II, Chemistry, Manufacturing and Control Section, Shipping Validation. Although your submission includes transport simulation stability, you need to perform a shipping study that includes transport of the product from the manufacturing facility in Germany to a customer facility in the US. Please submit

a study protocol in your response to this letter and the results to CBER upon completion of the study.

25. Volume III, Batch Records. Please clarify if US licensed reagents are used in the in-process and lot release testing of your products. If these reagents are not US licensed, please explain how you qualified the use of these reagents.
26. Volume III, Anti-S Monoclonal, Clone Raw Material. Please submit the English translation of these documents, including the translation of the handwritten comments.
27. Volume III, Anti-S Monoclonal, Batch Records. It appears that you did not provide the English translation of e.g., Anlage 1 zu SV-DS: Q-3042-04. Please review the batch records and submit the English translation of the documents written in German whose English translations have not been submitted.
28. Volume III, Anti- Jk^b Monoclonal, Batch Records, page 98. Please provide the English translation of the handwritten comments next to the labeling.
29. Volume III, Anti-S Monoclonal, Appendix 15, pages 5 and 6. Please submit the English translation of these documents, including the translation of the handwritten comments. Chemistry, Manufacturing and Control Section, Shipping Validation.
30. Please submit the summary of the open stability validation of each of the products.

Recommendation:

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