M E M O R A N D U M

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

Date: February 14, 2007

To: Files of STNs 125212/0 and 125214/0

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

Subject: Review memo: Biotest AG's Blood Grouping Reagents Anti-Fy[a] (Monoclonal) and Anti-s (Monoclonal)

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

Background:

Biotest AG, located in Dreieich, Germany submitted these applications for the manufacture of Seraclone® Blood Grouping Reagents (BGR) Anti-Fy[a] (Monoclonal) and Anti-s (Monoclonal) which are intended for typing blood specimens using manual tube agglutination methods.

Regulatory documents in the submission include Form FDA 356h, draft labeling, chemistry, manufacturing and controls, establishment information, stability data, and batch records (Anti-Fy[a], lot [redacted] and Anti-s, lot [redacted]

Review:

Manufacturing Summary

The Anti-Fy[a] (Monoclonal) (IgG) (For Further Manufacturing Use) [FFMU] and Anti-s (Monoclonal) (IgG) (For Further Manufacturing Use) material are supplied by Diagast under a shared manufacturing agreement with Biotest AG. The license applications for these FFMU products have been submitted to the FDA.

The table below 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	P3YAN3	Human IgG	2 ml x 1	0.1% NaN_3	24 months
Seraclone® Anti-Fy^a	DG-FYA-02	Human IgG	2ml x 1	0.1% NaN_3	24 months

* Six (6) month real time stability data support the shelf life of Anti-s. There are no stability data available to date for the Anti-Fy^a.

The potency specification for the Blood Grouping Reagents (BGR) Anti-Fy^a (Monoclonal) (IgG) and Anti-s (Monoclonal) (IgG) is [redacted].

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 Biotest's Anti-Fy^a (Monoclonal) and Anti-s (Monoclonal).

Trial Reagent	Number in Agreement	Number of tests	% Agreement	Lower 95% Confidence Limit
Anti-s (P3YAN3)	230	230	100%	98.7%
Anti-Fy^a (DG-FYA-02)	237	237	100%	98.9%

Review Questions:

Questions and Comments are written to address the sponsor directly.

1. Please note that we will inform you when to submit the test data, lot release samples, and protocols for the three (3) 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. The Anti-Fy^a (Monoclonal) (IgG) (For Further Manufacturing Use) [FFMU] and Anti-s (Monoclonal) (IgG) (FFMU) used for the Biotest Blood Grouping Reagent Anti-Fy^a (Monoclonal) (IgG) and Anti-s (Monoclonal) (IgG) manufactured by Diagast contain sodium azide as well as sodium arsenite. The sodium azide specification for both the Biotest Anti-Fy^a (Monoclonal) (IgG) and Anti-s (Monoclonal) (IgG) is 0.1%. Please explain how you can ensure that the concentration of sodium azide in the final container product is within the specification of 0.1%.

3. Volume I, Summary, page 4 of 11. This section states, "The filtered bulk products are sublotted and stored prior to vial filling." Also, "The QC testing data of final product from each sublot bottle is trended 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.

4. 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.*

5. 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.

6. 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.

7. Volume I, Summary, Sensitivity/Specificity, page 10 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.

8. 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 Us*e, 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 Us*e, 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."

9. 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 Us*e, it has to have an English translation on every label (other than the PI) it appears.

10. Volume, I, Package Inserts, Anti-Fy^{a} 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-s package insert includes the following statement: "Antibodies to the s antigen usually occur following immunization and are capable of causing hemolytic disease of the fetus and 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 by adding the required information per 21 CFR section 809.10 (b)(3).

d) The Summary section of the Anti-Fy^{a} package insert includes the following statement: "Antibodies to the Fy^{a} antigen are of the IgG class. Anti- Fy^{a} may cause hemolytic disease of the fetus and newborn (HDFN) and has been implicated in 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 by 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) Materials required but not provided section. Anti-human globulin is one of the materials that are listed under this section. Which anti-human globulin reagents have you tested for use with your reagents? Based on your data, do these anti-human globulin reagents work equally well with your reagents?

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 Us*e, it has to have an English translation on every label (other than the PI) it appears.

i) [redacted]

j) Under "Note", please replace the statement "Manage waste according to national guidelines" with "Manage waste according to local, state and national regulations".

k) Title 21 CFR 809.10 (b)(12) requires that the package insert include the specific performance characteristics describing the accuracy, precision, sensitivity and specificity of the product as appropriate. This section should include a statement summarizing the data upon which the specific performance characteristics are based. You should also include a telephone number that customers can call if additional information regarding testing performed at the time of manufacture is needed.

11. 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.

12. 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.

13. 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.

14. 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 CRF 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.

15. 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.

16. 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 (30) samples 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 that you perform additional testing in at least one other site.

17. 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."

18. Volume II, Chemistry, Manufacturing and Control Section, Container/Closure System, pages 23 - 24. Please clarify if you have performed [redacted] studies on the closure system for your products that are being considered for licensure.

19. Volume II, Final Product Real Time Studies, page 28. The proposed shelf life for the Seraclone® Anti-Fy^{a} is 24 months but there is no available real time stability data available to date. Please note that because you have not provided at least six (6) months of real time stability data for the Seraclone® Anti-Fy^{a}, we will be not be able to grant you a 24 month dating period for this reagent. Please submit at least the (6) months of real time stability data for the Seraclone® Anti-Fy^{a} to obtain approval for a 24 month dating period.

20. Volume II, CMC Section, Validation of Stability Test Methods, page 29. This section states, "The Blood Grouping Reagents are tested for specificity and potency using [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.

21. Volume II, Appendix 1, Certificates of Conformity, pages 1 and 3. These certificates of conformity indicate that sodium azide (at a final concentration of [redacted] and sodium arsenite (at a final concentration of [redacted] are the preservatives in the Seraclone® Anti-Fy[a] and Seraclone® Anti-s. The labeling for these products indicate that the preservative used is sodium azide only. Please comment. Please note that if sodium arsenite is used as a preservative, it should be stated in the labeling as required by 21 CFR 809.10.

22. 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.

23. 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 [redacted] Please explain how you determine that

24. 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.

25. Volume II, Appendix 13, Document SV-DS:Q-0100-00/10. This document is written in German. Please submit an English translation of the document.

26. Volume II, Appendix 14, DPPQF, Anti-s, Protocol for Approval, 3.4. Please explain why two (2) different refrigerated temperatures, i.e., 2…8ºC and 2…9ºC are in this section.

27. Volume II, Appendix 14, DPPQF, Stability report for Anti-s (MNS4), page 14 and 15. Our definition of the potency titer is the reciprocal of the greatest reagent dilution for which the reaction is graded as 1+. You perform the reciprocal titer by [redacted] Please explain how PRT of [redacted] translate to the standard titer measurement as we have defined above.

28. Volume III, Batch Records for Anti-Fy^a. Please explain why you had not submitted the batch records for at least one (1) lot of Anti-Fy^a.

29. 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.

30. Volume III, Appendix 16, Enclosure 16 to SV-D:P-001-00, Table for determination of the sample number, page 30. Please explain how you use the tables in this document.

31. 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.

32. Please submit the summary of the open vial stability validation of each of the products.

Recommendation:

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