

# **Review Memo - Biotest AG Blood Grouping Reagents - Seraclone Anti-s (Monoclonal)**

**Date:** December 19, 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<sup>a</sup> (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<sup>a</sup>(Monoclonal) and Anti-s (Monoclonal), which are intended for typing blood specimens using manual tube agglutination methods. The Anti-Fy<sup>a</sup> (Monoclonal) (IgG) (For Further Manufacturing Use) [FFMU] and Anti-s (Monoclonal) (IgG) (FFMU) materials 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 are being reviewed as companion submissions to the final container products.

CBER received the original submission dated September 22, 2006 on September 29, 2006. Regulatory documents in the submission include Form FDA 356h, draft labeling, chemistry, manufacturing and controls, establishment information, stability data, and batch records. Upon completion of the review, CBER issued a Complete Response (CR) letter on July 27, 2007.

This memorandum is a review of the amendment submitted by Biotest in response to the questions and comments conveyed in the CR letter. This memorandum does not address facility-related issues.

## **Chronology of Events:**

September 29, 2006 – Original submission dated September 22, 2006 received in CBER

July 27, 2007 – Complete Response letter issued

December 3, 2007 – November 30, 2007 response to CR letter received in CBER

## Review:

## Manufacturing Summary

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 <sub>3</sub> ----- Sodium arsenite	24 months
Seraclone ® Anti-Fy <sup>a</sup>	DG-FYA-02	Human IgG	2ml x 1	0.1% NaN <sub>3</sub>	24 months

[illegible]

The potency specification for the Blood Grouping Reagents (BGR) Anti-Fy<sup>a</sup>

(Monoclonal) (IgG) and Anti-s (Monoclonal) (IgG) is -----

## 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.

## Additional Testing

Biotest performed additional testing at FDA's request for Anti-M, Anti-N, Anti-S, Anti-s Anti-Fy<sup>a</sup>, Anti-P 1, Anti-Le a, Anti-k, Anti-Jk a, Anti- Jk b and Anti-E. The additional testing was performed at the Biotest Diagnostic Corporation facility in the U.S. and at the Biotest AG facility in Germany. Immucor reagents were used as reference reagents for the Biotest Anti-Fy<sup>a</sup> and Anti-s reagents.

The table below summarizes the rate of agreement for the Anti-s- (Monoclonal) and Anti-Fy<sup>a</sup> (Monoclonal) and the reference method.

### Combined Rate of Agreement (2006 and 2007 data)

<b>Trial Reagent</b>	<b>Number in Agreement</b>	<b>Number of tests</b>	<b>% Agreement</b>	<b>Lower 95% Confidence Limit</b>
Anti-s P3YAN3	360	360	100%	99.17%
Anti-Fy <sup>a</sup> - DG-FYA-	367	367	100%	99.19%

<b>Trial Reagent</b>	<b>Number in Agreement</b>	<b>Number of tests</b>	<b>% Agreement</b>	<b>Lower 95% Confidence Limit</b>
02				

In addition, the additional study was performed to meet the following objectives:

- Validate the use of other anti-human globulin reagents with Biotest's Anti-Fy<sup>a</sup> and Anti-s reagents
- Support the use of other anticoagulants other than EDTA
- Determine substances that could interfere with testing
- Support the testing of EDTA and clotted samples up to 10 days old and donor segments up to the unit's expiration date
- -----  
-----
- Obtain data on samples from elderly patients (>80 years old)
- Obtain data on samples with known red blood cell antibodies

Anticoagulant, interfering substances, sample age and sample storage studies were performed on representative products. These representative products were chosen based on the diluents used in the manufacturing of the products.

The results of the studies are summarized below:

**Sample Age Study:** There were no grouping discrepancies between the Biotest and the reference reagents.

**Hemolyzed Samples:** There were no grouping discrepancies between the Biotest and the reference reagents. The results prior to and after washing the red blood cells were identical.

**Icteric Samples:** There were no grouping discrepancies between the Biotest and the reference reagents. The results prior to and after washing the red blood cells were identical.

**Lipemic Samples:** There were no grouping discrepancies between the Biotest and the reference reagents. The results prior to and after washing the red blood cells were identical.

**Fresh and Stored EDTA and Clotted Samples with Reagents Red Blood Cells (RRBC) (Screening/Identification/Anti-Human Globulin):** The study demonstrated that Biotest RRBC and Biotest Anti-Human Globulin reagents can be used with fresh and stored (-----) EDTA anticoagulated and clotted samples.

**Fresh and Stored EDTA, Citrated and Clotted Samples with Blood Grouping Reagents:** Testing was performed using representative Biotest reagents, i.e., Anti-K, Anti-D, Anti-C, Anti-c, Anti-k and Anti-Le a. There was one sample tested with Anti-Le a that gave a discrepant result. Testing with a third method confirmed the positive results obtained with the Biotest reagent. A clotted sample that was also tested with Biotest Anti-Le a gave a false positive result.

**Anti-Human Globulin Anti-IgG Testing of Samples with Known Red Blood Cell Antibodies:** Ninety eight of the 101 samples were positive with both the Biotest and reference methods. An Anti-D and an Anti-Le a were not identified by the Biotest reagent but were identified by the reference method. A sample with a known Anti-Fy<sup>a</sup> did not react with either of the Biotest and reference methods. Two samples with Anti-M were identified by the Biotest reagent but were not detected by the reference reagent. The combined rate of agreement of the 2006 and 2007 studies is 99.27% (lower 95% confidence bound).

**Anti-Human Globulin Anti-IgG,-C3d; Polyspecific Testing of Samples with Known Red Blood Cell Antibodies:** One hundred one samples were tested. One sample with Anti-D, and two samples with Anti-M were not detected by the reference reagent. The combined rate of agreement of the 2006 and 2007 studies is 99.35% (lower 95% confidence bound).

**Sample from Patients that are >80 Years Old:** Only thirty eight samples could be procured for this study. Testing of the samples with a 2-cell RRBC screen and Anti-Human Globulin Anti-IgG and Anti-Human Globulin Anti-IgG,-C3d; Polyspecific yielded no discrepant results.

**Testing of Rare Antisera and Anti-E:** The combined rate of agreement (2006 and 2007 data) for each of the rare antisera and Anti-E is >99% (lower 95% confidence bound).

**Review of the Responses to the Product-related Questions Conveyed in the CR**

**Letter:** Questions and Comments are written to address the sponsor directly. A summary of Biotest's response is indicated by *italicized* text.

1. Please define and specify the range of room temperature in the Standard Operating Procedures. Reference is only made to "RT".  
*Biotest defines room temperature as -----.*
2. The Description of the Container Closure System states that the potency data provides evidence that there are no adverse effects, nor interfering substance that leeches out of the container/stopper system during the prolonged storage interval. Please provide an explanation of how no traces of escaped reagent is determined.  
*Biotest stated that the container closure integrity testing included -----  
----- Results of the potency, pH and protein testing were within the specifications at all time points.*
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.  
*Biotest evaluated -- shipments from Germany to the U.S. using ----- instead of the packaging material that have been in use for licensed products since 2005. The results demonstrated that the ----- is capable of maintaining the temperature of the package contents between ----- As a result of this evaluation, Biotest will perform a new shipping study and submitted the protocol for the transport validation of diagnostic products for overseas shipment. Biotest USA will perform a second shipping study to validate the shipment of the products from Biotest USA to the customer. Biotest submitted the shipping study protocols.*

**The protocol includes the evaluation of the temperature loggers in the packages. It does not include performance testing.**

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.  
*Biotest utilizes statistical analysis, trending of relevant process parameters and regular review of data to assure the production of product that consistently meets their pre-determined specifications and quality characteristics. Biotest referenced the SOPs pertaining to revalidation.*
5. Volume 1, Table III, page 3. It appears that the cell lines indicated in the table are incorrect. Please comment.  
*Biotest submitted a revised table with the correct cell lines.*
6. Please submit the draft of the lot release protocols for these products as soon as possible. Please note that we will inform you when to submit the test data, lot release samples, and final 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.  
*Biotest submitted a draft of the lot release protocol. Biotest needs to include the following information: the bioburden acceptance criterion, preservative, cell concentration, suspending medium, serum diluent and temperature. This could be conveyed to Biotest by telephone.*
7. The Anti-Fy<sup>a</sup> (Monoclonal) (IgG) (For Further Manufacturing Use) [FFMU] and Anti-s (Monoclonal) (IgG) (FFMU), manufactured by Diagast and used for the manufacture of Biotest Blood Grouping Reagent Anti-Fy<sup>a</sup> (Monoclonal) (IgG) and Anti-s (Monoclonal) (IgG), contain sodium azide as well as sodium arsenite. The sodium azide specification for both the Biotest Anti-Fy<sup>a</sup> (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%.  
*Biotest stated that the sodium azide concentration manufactured for Anti-Fy<sup>a</sup> (Monoclonal) (IgG) (FFMU) is ----- . During the production of the final container product the concentration of the sodium azide concentration is ----- to 0.1%.*
8. Volume I, Summary, page 4 of 11. This section states, "The filtered bulk products are sublotted and ----- vial filling." Also, "The QC testing data of final product from each subplot bottle is trended and reviewed to ensure that all subplot bottles are equivalent." Please describe how you perform subplotting of these products, including a description of the tests and their specifications to verify that each subplot 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.

9. Volume I, Summary, Rate of Agreement, page 7 of 11. The 95% lower confidence bound rate of agreement for Anti-s is 98.7% and the 95% lower confidence bound rate of agreement for Anti-Fy<sup>a</sup> is 98.9%. Your statistical requirement for equivalence of the trial reagents to the approved reference reagents is that the rate of agreement should be at least 98.5%. The rate of agreement for Anti- Jk a is 98.9%. Please note that although it is not a requirement, we expect the rate of agreement between the new and the reference reagents to be at least 99% (95% lower confidence bound).  
*Biotech performed additional testing in 2007. The combined rate of agreement from the 2006 and 2007 data are as follows:*  
*Anti-s - 99.17% (lower 95% confidence bound)*  
*Anti-Fy<sup>a</sup> – 99.19 % (lower 95% confidence bound)*

10. Please clarify if each of the lots used in the field 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 FDA Guidance, *Points to Consider in the Manufacture of In Vitro Monoclonal Antibody Products for Further Manufacturing Into Blood Grouping Reagent and Anti-Human Globulin*.  
*Biotest was not aware of this recommendation and did not manufacture each of the lots from a separate batch of antibody. Biotest provided a summary of successful production of historic lots to demonstrate Biotest's experience and expertise in manufacturing these products.*
11. 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.  
*Biotest submitted the summary of potency testing of three lots each of Anti-s and Anti-Fy<sup>a</sup>. These lots were not made from separate working cell bank vials but the lots met the potency specifications.*
12. 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 and explain how they differentiate the reagents from each other.

*There is no specific identity test performed for each product. However, in-process testing is preformed at various phases of the manufacturing process to ensure the correct identity of the final container product.*

13. 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.

*Biotest did not perform a separate study using a gold standard.*

14. 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.

*Biotest stated that they investigated all NTD and discrepant results. The only NTD results occurred when testing ABO reagents (forward and reverse typing discrepancy) and when testing Anti-D reagents (result of the negative Seraclone ABO/Rh control was positive).*

15. 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.

*According to Biotest, the calculation of the rate of agreement was erroneously stated in the original submission. The calculations were based upon the comparison between the initial test results and the reference test results.*

16. 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.  
*The TANGO components were included by mistake.*
17. 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. Title 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.  
*Biotest will retain the records for at least three years after completion of the trial.*
18. 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.  
*Biotest submitted the missing documents.*
19. 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 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 additional site.  
*Additional testing was performed at the Biotest facilities in the U.S. and Germany.*
20. Volume II, Chemistry , Manufacturing and Control Section, Container/Closure System, pages 23 - 24. Please clarify if you have performed ----- studies on the closure system for your products that are being considered for licensure.  
*Biotest stated that they performed ----- testing as part of the validation of the ----- automatic filling machine. ----- studies were also conducted in 2004 and 2006.*
21. Volume II, Final Product Real Time Studies, page 28. The proposed shelf life for the Seraclone® Anti-Fy<sup>a</sup> 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<sup>a</sup>, we will be not be able to grant you a 24 month dating period for this reagent. Please submit at least (6) months of real time stability data for the Seraclone® Anti-Fy<sup>a</sup> to obtain approval for a 24 month dating period.  
*Biotest submitted a graphs summarizing the stability testing of Seraclone® Anti-Fy<sup>a</sup> up to 12 months. The final testing time point is scheduled for July 2008.*

22. 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 standard -----  
-----". 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.  
*Biotest stated that they have a viable training and competency assessments programs including testing of survey materials by the testing staff.*
23. Volume II, Appendix 1, Certificates of Conformity, pages 1 and 3. These certificates of conformity indicate that sodium azide (at a final concentration of -----) and sodium arsenite (at a final concentration of -----) are the preservatives in the Seraclone® Anti-Fy<sup>a</sup> 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.  
*According to Biotest, -----  
-----*  
*-----*. *Biotest calculated the final concentration of the sodium arsenite and will include it in the labeling.*
24. 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.  
*Biotest provided the English translation of the documents.*
25. 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.  
*Biotest provided the English translation of the document.*
26. Chemistry, Manufacturing and Controls section. The incoming in-vitro substance human/----- monoclonal antibodies are tested for -----  
. Please provide your rationale for performing these tests.  
*As a precaution, Biotest performs ----- once for monoclonal antibodies.*

27. Chemistry, Manufacturing and Controls Section. Please provide a description for the diluents that you used to manufacture Blood Grouping Reagents. You must also include this or a generic description in your package inserts under the Reagents section.  
*The diluents for Anti-s and Anti-Fy<sup>a</sup> are buffered protein solutions containing bovine albumin and macromolecular potentiators. These diluents are listed under the Reagent section of the package insert.*
28. 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.  
*Biotest provided the English translation of the document.*
29. Volume II, Appendix 14, DPPQF, Anti-s, Protocol for Approval, 3.4. Please explain why two (2) different refrigerated temperatures, i.e., 2...8°C and 2...9°C are in this section.  
*The correct refrigerated temperature is 2...8°C.*
30. 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 -----  
----- . Please explain how PRT of ----- translate to the standard titer measurement as we have defined above.  
*Biotest stated that in the stability report for Anti-s, the titer was not performed by -----  
----- . The scale of the graphs should have been the titer dilutions --, -----  
----- . The potency titers are -----.*
31. Volume III, Batch Records for Anti-Fy<sup>a</sup>. Please explain why you had not submitted the batch records for at least one (1) lot of Anti-Fy<sup>a</sup>.  
*Biotest has submitted the batch records for Anti-Fy<sup>a</sup>.*
32. 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.  
*U.S. licensed products are not used for in-process testing. Test reagents are tested against a standard which is a current released lot of product. The potency of the reference material is in accordance with 21 CFR 660.25 (a) and CBER's recommended methods.*
33. 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.  
*The Table for determination of the number of samples is used in conjunction with Enclosure 14, Finished Product Inspection, of SV-D:P-001-00. Based on the results of*

*the previously produced lots the test severity is set as “reduced”, “standard” or “intensified” in Enclosure 14. The number of samples to be taken is listed in Enclosure 14 based on the overall batch size. As soon as the batch size is entered in the line “Batch size” on Enclosure 16, the ranges within the batch to be sampled are listed in the appropriate column.*

34. Please submit the summary of the open vial stability validation of each of the products. *Biotest submitted a graphical summary of the stability data for Anti-Fy<sup>a</sup> and Anti-s. The stability on the Anti-Fy<sup>a</sup> reagent has been validated to 12 months. The final testing interval is scheduled for July 2008. Stability testing on the Anti-s was scheduled to be completed in November 2007.*

## **LABELING**

35. Title 21 CFR 801.437(d) requires the following statement on all labels and labeling for devices that contain natural rubber, “Caution: This product contains Natural Rubber Latex Which May Cause Allergic Reactions.” *Biotest has revised the label to include the aforementioned statement.*

36. 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 FDA 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. *The symbol ACT has been replaced with “Meets FDA Potency Requirements”.*
- b. The symbol you use for preservative is the word PRES in a box. Since it is not listed in the FDA 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. *The symbol PRES in a box has been deleted from the vial for lack of space.*
- c. Please replace “FDA Lic.” with “U.S. License” or “U.S. License Number.” *“FDA Lic.” has been replaced with “ U.S. License No.”*

37. Volume I, DRAFT Labeling, Carton Label.

- a. Please replace “FDA Lic.” with “U.S. License” or “U.S. License Number.”  
*“FDA Lic.” has been replaced with “ U.S. License No.”*  
*Because of space limitations, Biotest is requesting an exemption from the requirement of 21 CFR 660.28 (a)(3) that the type size for the specificity of the antibody designation on the labels of the final container with a capacity of less than 5 ml be at least 12 point and the type size for container with a capacity of 5 ml or more be at least 18 point. The type size of Biotest containers with 5 ml and 10 ml capacities is 12 point instead of 18 point.*
- b. The symbol you use for preservative is the word PRES in a box. Since it is not listed in the FDA 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.  
*The symbol PRES in a box has been replaced with the word “Preservative”.*

38. Volume I, Package Inserts, Anti-Fy<sup>a</sup> and Anti-s.

- a. Please replace “FDA License” with “U.S. License” or “U.S. License Number.”  
*“FDA Lic.” has been replaced with “ U.S. License No.”*
- 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.”  
*The word “characteristics” under the Intended Use section has been replaced with the word “antigen”.*
- c. Materials required but not provided section of the Anti-Fy<sup>a</sup> package insert. Please add IgG coated red blood cells to this section since these cells are used in the test procedure.  
*Biotest has added IgG coated cells to the Materials required but not provided section. Biotest also listed IgG coated red blood cells (e.g. Biotest Coombscell-E). This product has not been cleared and should not be mentioned in the package insert.*
- d. 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 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 809.10 (b)(3).

*Biotest has revised the Summary section to comply with 21 CFR 809.10 (b)(3).*

- e. The Summary section of the Anti-Fy<sup>a</sup> package insert includes the following statement: “Antibodies to the Fy<sup>a</sup> antigen are of the IgG class. Anti- Fy<sup>a</sup> may cause hemolytic disease of the fetus and newborn (HDFN) and has been implicated in hemolytic transfusion reactions (HTR). 1” Title 21 CFR 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 809.10 (b)(3).

*Biotest has revised the Summary section to comply with 21 CFR 809.10 (b)(3).*

- f. 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.

*Biotest performed additional testing to collect data on clotted and various anticoagulated samples. See results of the study under Additional Testing.*

- g. Under “Materials required but not provided”, please specify the dimensions of the tubes that should be used.

*Biotest has specified the dimensions of the tubes under the “Materials required but not provided” section.*

- h. 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?

*Biotest performed parallel testing of the Biotest anti-human globulin reagent and FDA licensed reagents and found no discrepancies in the test results. Biotest lists the Biotest anti-human globulin reagent (along with the product reference number) in the package insert as an example of an acceptable anti-human globulin reagent.*

- i. Glossary of Symbols. Please include “ACT” and its definition in the table. Moreover, since it is not listed in the FDA 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. *The symbol ACT has been removed from the labeling and replaced with “Meets FDA Potency Requirements”.*

- j. -----  
-----  
-----  
-----  
-----.

*Biotest opted to remove reference to -----  
-----.*

- k. Under “Note”, please replace the statement “Manage waste according to national guidelines” with “Manage waste according to local, state and national regulations”.

*Biotest has replaced the above statement per FDA’s recommendation.*

- l. 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.

*Biotest has revised the specific performance characteristics section as recommended.*

## **Recommendation:**

The responses are acceptable except for the following issues:

1. Forms FDA 2567 indicate that Seraclone ® Anti-Fy<sup>a</sup> and Anti-s are -----monoclonal in origin. Both the container and the package insert indicate that these two reagents are human monoclonal in origin. Please clarify and make the necessary corrections.



2. You listed Biotest Coombscell-E in the package insert as an example the IgG coated red blood cells that can be used to verify negative reactions in an antiglobulin test. Please note that Biotest Coombscell-E has not been cleared and should not be mentioned in the package insert. Please remove reference to the Biotest Coombscell-E and submit the revised package insert.
3. Please revise the lot release protocol template to include the bioburden acceptance criterion and the following information: preservative, cell concentration, suspending medium, serum diluent and temperature.
4. Please submit the results of the stability studies when they become available.
5. Please submit the results of the shipping studies when completed.

I recommend that CBER communicate these issues to Biotest by telephone.