DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852-1448

Our STNs: BL 125216/0 and 125217/0

July 27, 2007

Biotest AG
Attention: Mr. William Weiss
Biotest Diagnostics Corporation
66 Ford Road, Suite 220
Denville, NJ 07834

Dear Mr. Weiss:

We have completed the review of your submissions dated September 22, 2007 to your biologics license applications (BLA) for the licensure of Blood Grouping Reagents Anti-S (Monoclonal) and Anti-Jk^{b} (Monoclonal) submitted under section 351 of the Public Health Service Act.

The deficiencies in CMC/CLINCAL/STATISTICS/LABELING are as follows:

CMC/CLINICAL/STATISTICS

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 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.

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. Conformance lots for Anti-S and Anti-Jk^b. Please submit the draft of the lot release protocols 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.

8. 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 these 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.

9. 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.

10. Volume I, Summary, Rate of Agreement, pages 7 and 8 of 11. The statistical requirement for equivalence of the trial reagents to the approved reference reagents in that the rate of agreement should be at least 98.5% (95% lower confidence bound). The 95% lower confidence rate of agreement for Anti-S is 98.7% and the 95% lower confidence bound rate of agreement for Anti-Jk^b 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).

11. 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.

12. 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.*

13. 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.

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.

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.

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.

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 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.

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.

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 field trial testing in at least one additional site.

20. 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."

21. 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 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.

22. Volume II, Chemistry, Manufacturing and Control Section, 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.

23. 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 why you chose 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]

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

    a) Please explain why you chose a [redacted] in some of your serological tests.

    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]

25. 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.
26. 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.

27. Chemistry, Manufacturing and Control Section. The incoming in-vitro substance human/mouse monoclonal antibodies are tested for [redacted] Please provide your rationale for performing these tests.

28. Chemistry, Manufacturing and Controls section, page 99. 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.

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, Anti-S Monoclonal, Clone Raw Material. Please submit the English translation of these documents, including the translation of the handwritten comments.

31. Volume III, Anti-S Monoclonal, Batch Records. It appears that you did not provide the English translation of 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.

32. Volume III, Anti- Jk^b Monoclonal, Batch Records, page 98. Please provide the English translation of the handwritten comments next to the labeling.

33. 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.

34. Please submit the summary of the open stability validation of each of the products.

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.”

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 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 FDA 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. License" or "U.S. License Number."

37. Volume I, Draft Labeling, Carton Label.

    a) Please replace "FDA Lic." with "U.S. License" or "U.S. License Number."

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

38. Volume, I, Package Inserts, Anti-Jk[a] and Anti-Jk[b] and Anti-S.

    a) Please replace "FDA License" with "U.S. License" or "U.S. License Number."

    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-Kidd 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 anemnestic response to the Kidd antigen.[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).

    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 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).

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

i) 

j) 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.

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.

Please note that we have had to request English translation of numerous documents in these submissions and that we have made this same request during the review of other current submissions as well as previous submissions. Future submissions containing foreign-language text that is not translated into English are subject to "refusal to file" as described in CBER SOPP 8404 - Refusal to File Procedures for Biologic License Applications, available at http://www.fda.gov/cber/regsopp/8404.htm.
We reserve further comment on the proposed labeling until the applications are otherwise acceptable. We may have comments when we see the proposed final labeling.

Should additional information relating to the safety and effectiveness of these products become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. For PDUFA products please submit your meeting request as described in the FDA Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products February, 2000 (http://www.fda.gov/cber/gdlns/mtpdufa.pdf). For Non PDUFA products, please contact the regulatory project manager. For details, please also follow the instructions described in CBER's SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants (http://www.fda.gov/cber/regsopp/81011.htm).

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the applications; (2) notify us of your intent to file amendments; or (3) withdraw the applications.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

If you have any questions, please contact the Consumer Safety Officer, Teresita C. Mercado, at (301) 827-6139.

Sincerely yours,

Elizabeth Callaghan
Acting Director
Division of Blood Applications
Office of Blood
Research and Review
Center for Biologics
Evaluation and Research