

Rana, Pratibha

From: Rana, Pratibha
Sent: Thursday, April 07, 2011 4:27 PM
To: 'Matthew Vaughn'
Subject: STN 125389/0 Information Request I/ April 7 2011

To: Matthew Vaughn Biotest Pharmaceuticals Corporation

This is regarding your BLA submission STN 125389/0 for Immune Globulin Intravenous (Human), submitted to the Agency on November 3, 2010. FDA continues with the review of the referenced submission and requests BPC to provide the following information.

1. Please verify which testing laboratories are going to perform the following release tests:
 - a. Are the tests for Appearance and Sterility performed solely at Biotest and/or, in addition, at (b)(4) (as with Nabi-HB)?
 - b. Is (b)(4) going to be an alternate/back-up testing laboratory for the (b)(4) purity (protein composition) test?
 - c. Is the pyrogenicity test performed solely at (b)(4) or will (b)(4) serve as an alternate/back-up testing laboratory?
2.
 - a. Please propose a specification for Total IgA in the Biotest-IGIV (i.e., specify an amount or limit) based on your conformance lot data.
 - b. Please commit to setting the Total IgA release specification for Biotest-IGIV (b)(4) after manufacturing a minimum of 12 full-scale commercial lots.
3. Please revise the wording of your specifications for:
 - a. (b)(4)
 - b. (b)(4)
4. Your diphtheria antitoxin specification is currently expressed in "IU/mL", not in "units (U)/mL". It is also not apparent in your method SOP about which reference standard you are using.
 - a. Please use the US Standard Diphtheria Antitoxin for revalidation and revise your specification such that it is expressed as "U/mL". The minimum ratio for a 16.5% IgG solution is 2 U/mL; hence, the adjusted ratio for Biotest-IGIV should be approximately (b)(4) U/mL.
 - b. Please submit the revalidation study data and include the conversion ratio between IU and U.
5. Your anti-measles antibody specification is currently set at " $\geq 0.60 \times \text{Ref (176 CBER)}$ ". Please take note that FDA CBER has allowed manufacturers to lower their anti-measles antibody specification from " $\geq 0.60 \times \text{Ref (176 CBER)}$ " to " $\geq 0.48 \times \text{Ref (176 CBER)}$ " due to the observed trend of declining anti-measles titers in the US donor population (Audet, S. *et al*, J. Infect. Dis. 2006; 194:781-9) - provided that they submit the change as a Prior Approval Supplement and agree to do the following: a) report measles in a PID patient as a 15-day adverse event report; b) labeling changes to address dosage adjustments for patients with actual or potential exposure to measles; and c) a postmarketing commitment to measure trough levels in a patient receiving a known dose of measles antibodies (may be done in the context of a previous, ongoing or planned efficacy trial)(see May 1-2, 2008 Blood Products Advisory Committee presentation: http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4355S1-6_files/frame.htm).
6. You did not set specifications for albumin and plasmin/plasminogen impurities in the final product, stating that the levels are extremely low or undetectable. However, we recommend that you propose specifications for these two impurities in order to ensure safety and purity of Biotest-IGIV. In addition, please submit the supporting method SOPs and method validation studies.
7. You also did not set specifications for (b)(4) and heat stability. Please propose specifications for these parameters

and submit the supporting method SOPs and method validation studies.

8. We recommend that you check the May 2010 FDA Guidance for Industry, “Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Product”, for the recommended wording for the Warning Section. Please revise your Warning and Precautions sections on pages 1 and 3 accordingly.
9. Please include a statement on parvovirus B19 NAT testing and the B19 DNA manufacturing pool limit in Section 11, Description (second paragraph) of your package insert, e.g., “*NAT for parvovirus B19 (B19) DNA is also performed on pooled samples of all Source Plasma and the limit for B19 DNA in a manufacturing pool is set not to exceed 10^4 IU/mL*”.
10. What do you consider as the “date of manufacture” for each Bivigam lot?

Please submit a response to this request as an amendment to the file by May 9, 2011.

Thank you.

Pratibha Rana

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