

Bayer HealthCare
Biological Products Division



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Vice President
Worldwide Regulatory Affairs
Responsible Head/Agent

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Comments on Factor VIII Inhibitor Workshop
Docket number 2004N-0033

Dear Dr. Lozier,

Bayer HealthCare LLC, Biological Products Division submits the following comments and suggestions regarding the topics discussed at the recent Workshop on Factor VIII Inhibitors.

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Use of Plasma-Derived FVIII as a Standard for the Performance of Clinical Trials

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During the workshop it was proposed that plasma-derived FVIII serve as the standard against which new FVIII drug products would be compared in bioequivalence studies. In our view, use of plasma-derived FVIII poses significant concerns for patient recruitment. Although plasma-derived products are considered safe at present, patients may prefer not to be exposed to the theoretical or potential risks entailed by use of plasma-derived FVIII. In our experience, significant numbers of patients have taken the decision to receive solely recombinant products so as to mitigate the theoretical risks associated with the use of plasma-derived FVIII. Patient recruitment may be especially affected in patient populations which have never been exposed to plasma-derived FVIII. This would especially be critical for pharmacokinetic studies in general, in which no benefit can be expected. This point was made by several investigators during the workshop, and we support their position.

We are also concerned about which plasma-derived FVIII product may be chosen for comparison to a new product. Until it has been demonstrated that different plasma-derived FVIII products exhibit the same or similar PK profiles it would be premature to require that a plasma-derived Factor VIII be used as the comparator in

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bioequivalence studies. Depending upon the plasma-derived product chosen it might lead to false conclusions about the suitability of a new product.

Bioequivalence studies

In discussing clinical trials supporting the licensure of new FVIII products, the FDA proposed that sponsors conduct bioequivalence studies in accordance with the requirements established for chemical drugs (i.e., that the 90% confidence interval of the ratio of the test product to the reference product be within the boundaries of 0.80 – 1.25 for the primary PK parameters). While Bayer agrees that a pharmacokinetic study may be needed to describe the distribution, metabolism and elimination of the new entity in comparison to a known standard, we do not see the necessity of a formal bioequivalence study comparison between the new product and a reference product. Instead, Bayer suggests that new FVIII products achieve predefined pharmacokinetic properties and parameters in a well-designed clinical study, such that the C_{max} (or 10 minutes recovery) and half life values obtained are considered acceptable by the scientific community for an efficacious FVIII product.

Exposure Days (ED) of Previously Treated Patients (PTPs)

Significant discussion during the workshop was given to the eligibility criterion of the number of exposure days (EDs) for enrollment of patients into PTP clinical trials. While Bayer agrees that the risk for inhibitor formation is slightly higher after 150 ED than after 250 ED, this risk is substantially lower when compared to fewer exposure days, such as 50-100 ED. The change in the risk profile was described by C. McMillan et al. (Blood 71:344-348, 1988) who showed the asymptotic rise in the plot of inhibitor formation risk versus the exposure day. Based on these studies, recommendations for an increase in exposure days to 250 ED as an eligibility criterion in PTP studies would only slightly reduce the risk of inhibitor formation while unnecessarily impairing patient enrollment. Reducing the number of ED to the range of 50-100 ED would also not be advisable because it may represent an increased risk for inhibitor formation which could confound identification of product-related versus patient-related inhibitor formation. Consequently Bayer requests that the current recommendation of 150 ED be maintained as an eligibility requirement for patient enrollment in PTP clinical trials.

Study failure or project failure based upon the number of patients developing an inhibitor

While Bayer agrees with the FDA that the statistical validity of a sample size calculation be based on the currently accepted level of inhibitor formation, we disagree that the finding of a second inhibitor case should automatically be considered a failure criterion of the clinical trial and subsequently of the experimental FVIII product. The workshop discussions of the so called Dutch

and Belgian publications showed that FVIII products with immunogenic properties are most likely to generate clusters of patients with inhibitor formation rather than single sporadic cases. Since inhibitor formation in PTPs may be a multifactorial event and not completely understood, we propose that the occurrence of a second inhibitor case during the clinical trial should result in a discussion among the Agency, Sponsor, and experts as to the possible causes rather than an automatic trial and product failure.

Written Guidelines

We encourage the Agency to publish their current thinking as a draft guidance for public comment. We believe this would contribute to increased discussion and identification of common understandings among all stakeholders involved in drug development for Hemophilia products. This will add homogeneity and objectivity in the requirements as well as valuable help in planning clinical trials.

International Harmonization

We applaud the FDA and its initiative to pursue international harmonization among regulatory agencies to establish harmonized criteria and requirements for Factor VIII drug development.

Sincerely,



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