Caroline J Loew, PhD
Vice President
Scientific and Regulatory Affairs

PhRMA

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5630 Fishers Lane, rm. 1061
Rockville
MD 20852

PhRMA Additional Comments for Docket # 2004N-0355

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA members invested an estimated $38.8 billion in 2004 in discovering and developing new medicines. PhRMA companies are leading the way in the search for cures.

PhRMA wishes to thank FDA for this opportunity to supplement the comments previously submitted to the docket. PhRMA also wishes to thank FDA for its role in organizing and conducting the FDA/DIA Scientific Workshop on Follow-On Protein Pharmaceuticals. In general, PhRMA believes that the Workshop was a productive meeting that advanced in a transparent way the knowledge of various aspects of the science of follow-on biologics.[1] There appeared to be an emerging, though not completely agreed, consensus that the "generic" model used for small molecule drugs – i.e., that sameness and bioequivalence justifies an abbreviated approval – is not suitable for application to biologics. Rather, unique safety and efficacy considerations of biologics make them unsuitable for this approach, as described at length in PhRMA's previous submission and highlighted here.

The following are additional comments to the docket based on statements made, and issues raised, during that Workshop.[2]

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[1] As used in this document, the term "follow-on biologic" means a biological product for which FDA approval would rely in part on the safety and effectiveness of similar already-approved products developed by other, unrelated manufacturers. It encompasses products for which the innovator was approved under either the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act. Although the Workshops referred to follow-on protein products, that term is included in follow-on biologics.

[2] At the Workshop, Steven Kozlowski of FDA suggested that there was "Flexibility in [the] PHS Act" for FDA action on follow-on biologics. PhRMA previously addressed the legal issues concerning follow-on biologics in its November 12, 2004 submission to FDA docket # 2004P-0171, which was Attachment B to PhRMA's November 12, 2004 submission to docket # 2004N-0355.

1. Appropriate Safety Monitoring and Pharmacovigilance are Critical

At the Workshop, representatives of some generic companies appeared to minimize the potential safety issues raised by approval of follow-on biologics, including the importance of post-marketing safety studies for each product. Immunogenicity is, for example, one significant potential safety issue for both innovator and follow-on biologics that must be studied in both the pre- and post-marketing phases of product life. Immunogenicity, however, is not the only safety concern. Innovator companies invest substantial resources in both the development and post-marketing phases to evaluating not only rare, unexpected events, but also to ensuring that the safety profile and label of products accurately reflects adverse drug reactions first detected in the pre-market phase, as well as any detected in the post-marketing environment. If follow-on biologics were approved, the choice of physicians and patients among products would need to be based on full knowledge of expected adverse events and their frequency. For example, if thromboembolism or hypertension is present at a certain rate with an innovator product, the physician and patient need to be able to assess whether a follow-on biologic would have a similar or different expected safety profile. It is thus critical that the manufacturers of follow-on biologics engage in appropriate safety assessments of their products both during development and, once marketed, through post-marketing surveillance.

The potential problems with safety monitoring and pharmacovigilance would be magnified greatly if it were determined that follow-on products could be interchangeable, or substitutable. In addressing this issue, it is imperative to be able to distinguish each follow-on biologic by a unique International Non-Proprietary Name (INN) so that safety data can be associated with specific products, whether innovator or follow-on biologics. It will be important for the physician to be involved in any decision regarding use in order to assure that patients receive the best therapy for their specific medical situation. In addition, unique INNs will be critical to support tracking for the purposes of post-approval safety monitoring.

2. The Manufacturing Technology Used By Innovator Manufacturers Is Not an Issue

During the Workshop, representatives of some generic companies asserted that innovator manufacturing processes were older than for proposed follow-on biologics, and that they are not modernized over time. The implication was that, because generic applicants would be submitting process information later in time for a given biologic, generic processes would be more modern, and that generic products could even be of better "quality." Contrary to such suggestions, PhRMA notes that innovators often modernize the contents of their approved applications to incorporate new technologies and updated analytical methods. These updates are done continually throughout the lifecycle of the product based on the innovator's intimate knowledge of the product and the processes used to make it. Data to support these changes are provided to FDA, which determines the extent and appropriateness of the data before approval is granted to implement any particular change. The current regulatory expectation is that an approved application will contain sufficient data to ensure a safe, efficacious, and high quality product. The contents of each application have been deemed acceptable by FDA through their

review and approval. Whether this application is approved today, or was approved many years ago, FDA defines the appropriate data necessary to ensure that a high quality product is introduced in the market and is maintained to meet the regulatory expectations. In any event, if a follow-on manufacturer conducts comparative analytical studies, it must compare a potential follow-on product to the innovator product which is made by state-of-the-art methodology, which may not be the methodology that was in place at the time that the innovator product was first approved. In addition, it is important to note that, whether technology is old or new does not affect the issue whether a follow-on applicant can rely on the innovator's data, which is prohibited, as discussed in PhRMA's November 12, 2004 submission to the docket.

3. FDA Must Carefully Review the Applicability of Bioequivalence Concepts

As mentioned above, part of the current paradigm for approval of generic small molecule drugs is the concept that if a purported generic small molecule drug contains the same active ingredient (and the product is the "same" in other ways) as the innovator drug and it is absorbed to the same rate and to the same extent as the innovator product, the products will be considered bioequivalent and assumed to have an equivalent safety and efficacy profile. Part of the reason that the generic small molecule drug paradigm does not work well when applied to biologics is the difficulty in determining bioequivalence for biological drugs.

During the Workshop, a representative of a generic company cited 21 C.F.R. 320.22 and asserted that bioequivalence testing should not be required for biologics that are in parenteral solution. Dena Hixon of the FDA clarified that, while the regulation provides for the waiver of bioequivalence testing on certain small molecule drugs in solution, it does not create a general scientific rule that would be applicable to biologics. First, the solubility of proteins in solution is dependent on many inter-related factors, and is much more complex than the solubility parameters of small chemical drugs. Second, the regulation requires that the product have the same active and inactive ingredients in the same concentration as the innovator product, a criterion that few if any biologics could meet. Third, biologic drugs are often not a single homogeneous active substance in solution, and thus the assumption of bioequivalence for a small molecule drug in solution is invalid when applied to biologics. Furthermore, as was demonstrated by Mark Rogge's presentation at the Workshop, actual concentrations of products in various tissues may or may not be reflected by plasma concentrations. Thus, FDA may require pharmacokinetic (PK) and pharmacodynamic (PD) studies to study distribution in other tissues that might be expected to be affected by the biological product, and not just blood plasma levels. Given the complex mechanism of clearance for biologics and for accessing their sites of action, it is important to demonstrate PK and PD similarly to justify dosing in patients. Finally, PhRMA notes that the break-out sessions on pharmacology/toxicology generated a strong consensus that appropriate nonclinical (toxicology and pharmacokinetic) studies would be required for all new biologic products, including follow-on products. This differs from the conclusions of one presenter from FDA in the plenary session. The views of the FDA Pharm/Tox review groups were better represented by their participation in the break-out session, which recommended that pharmacology/toxicology studies be required for all new biologic products.

There was also a suggestion made at the Workshop that there could be wider statistical criteria for evaluating bioequivalence of follow-on products than that historically applied to small molecule drugs. There is no scientific basis to justify wider criteria for evaluating bioequivalence of biologics. Rather, to the extent that the concept of bioequivalence may be applicable to a follow-on biologic at all, due to the complexity of the products, potential impact of heterogeneity, and potential for immunogenicity, there are compelling reasons for FDA to ensure that the criteria for evaluating bioequivalence are as tight, or even narrower, than for small molecule drugs.

4. Data are Required for Each Indication

Innovator manufacturers generate data to substantiate each indication for their product as described on the product label, which supports use in the intended patient population and known mechanisms of action. Likewise, a follow-on biologic applicant would need to supply data to support each indication of its product. This is unlike the situation with typical generic small molecule drugs, where bioequivalence testing is typically based on a single mechanism of action and is often performed in healthy patients, or in a limited patient population. Adverse events, and sometimes efficacy, may differ in different patient populations. This situation may be more pronounced for biologics than for small molecule drugs because of the inherent heterogeneity of the products, differences in clearance, and other characteristics unique to biologics. In addition, some biological molecules may have different mechanisms of action at different target sites that are associated with efficacy related to different indications. In some cases, these mechanisms are not well defined. Even products with a similar mechanism of action may have different impurity profiles, or slight differences in product heterogeneity, that may not be important for treating one indication but may manifest as adverse events in another. The immunogenicity issue that arose with respect to Eprex is an important example. Although pure red cell aplasia occurred in some renal failure patients, it was not seen in cancer patients. Given the characteristics of biologics, it would not be scientifically supportable to approve a follow-on biologic based on data for one indication and then extrapolate that approval to all of the indications of the innovator product that may involve a different mechanism of action in a different population without appropriate supporting data generated using the follow-on product.

5. FDA Should Scrutinize the Precedential Value of Foreign Marketing

During the Workshop, a presenter from a generic company referred to follow-on biologics marketed abroad, suggesting that such cases are precedent for FDA action. Contrary to the suggestion of the comment, foreign marketing experience for a product, even the same product as is proposed to be marketed in the United States, should not be weighed heavily by FDA. Rather, it is important for FDA to be cautious and to consider for any foreign product the standards and scrutiny of the regulatory system under which it was approved, the data submitted to approve the product abroad, and the adequacy of the post-market surveillance system in the particular country. As FDA knows, there is a continuum of regulatory approval systems in foreign countries, with some not requiring substantial data submissions and some not including a

thorough scientific and medical review by experienced regulators. Given the limited regulatory oversight in some of these countries, the data sets may underreport safety risks which could have been identified under FDA and ICH pharmacovigilance standards. Significantly, none of the ICH countries has in place a framework for approval of follow-on biologics.

Yours sincerely,

Caroline J. Loew.