March 16, 2005

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 2004N-0355
Scientific Considerations Related to Developing Alternative Brand and Generic Biopharmaceuticals ("Follow-On Protein" Products)

Dear Sir or Madam:

The Generic Pharmaceutical Association (GPhA) submits the following comments to Docket No. 2004N-0355 Scientific Considerations Related to Developing Alternative Brand and Generic Biopharmaceuticals (referred to by FDA as "Follow-On" Protein Products) and the Federal Register Notice dated February 16, 2005, that announced this docket was reopened.

GPhA commends the FDA for seeking industry comments and hosting public forums on this important issue. Recent workshops, as well as public comments from FDA and industry leaders, have demonstrated that the science clearly supports immediate implementation of a definitive abbreviated approval pathway for generic biopharmaceuticals.

In particular, the February 14-16, 2005 DIA-FDA Scientific Workshop on Follow-on Protein Products addressed important issues relevant to the scientific approach for establishing this abbreviated approval process for biopharmaceuticals. Scientific topics included characterization, PK/PD, immunogenicity, animal pharmacology-toxicology, biological characterization and clinical safety and efficacy. Our comments will focus on these scientific topics, as well as address other considerations that were raised at the February 2005 Workshop.

As GPhA has previously stated, the question is not 'if' generic biopharmaceuticals will become a reality, but 'how' and 'when.' At GPhA's Annual Meeting on February 26, 2005, Acting FDA Commissioner Dr. Lester Crawford asserted, "I think we now have the science to fashion a generic biologics program." Dr. Crawford added that since the science exists, a regulatory policy to address a generic biologics program is now needed. GPhA fully agrees with that position.

The immediate implementation of a definitive abbreviated approval framework -- driven and supported by science -- must be based on the principles of comparability. This concept has been well established for nearly a decade, a point that was specifically acknowledged by FDA's Dr. Steven Kozlowski in a plenary session during the workshop. In fact, the FDA already relies on these principles to permit biopharmaceutical brand manufacturers to change the production process, cell line, manufacturing site, and formulation of many biologics, such as recombinant proteins and monoclonal antibodies, without clinical data supporting safety and efficacy. FDA has also permitted albumins and allergenics, among other products, to come to market with abbreviated data packages.

As Dr. Kozlowski asserted, under the FDA approach, "structure equals function." The more that is confirmed regarding structure, the more assurance there is regarding the function or effect of the product. Indeed, the scientific principles for comparability comparisons are valid for both brand products as well as generic biopharmaceuticals. The baseline of this approach starts with characterization. As presented during the recent workshop, current analytical capabilities allow for exquisite characterization of most protein products.

Not only has the technology to characterize proteins significantly progressed, but also the science and methods to characterize glycans. Current technology allows us to characterize simple to moderately complex glycan products. As for more complex products, the technology exists to build an "equivalence window" using a suite of commonly available analytical tools to establish product aspects that can define equivalence. It is possible to do this today, and we support this concept.

It is clear that there is not a one-size fits all approach for protein products; the complexity of protein products requires multi-faceted approaches. Analytical characterization, utilizing a portfolio of tools, is capable of determining the level of comparability of most protein products. These same tools, currently used by the brand industry to assess comparability before implementing changes, could readily be used to compare the physical, chemical, and biological parameters of affordable biopharmaceuticals and their brand counterparts. These analytical approaches, combined with FDA's expertise and judgment, allow both the applicant and FDA to make a risk assessment and to determine if additional testing is necessary. FDA should apply the same risk-based decision-making to all facets of the approval process for affordable biopharmaceuticals, including immunogenicity. If the product risk profile is the same -- or less -- FDA should be able to approve the product and provide consumers with a more affordable choice.

After a comprehensive analytical comparison, other testing may be necessary as determined on a case-by-case basis. Based on the hierarchy of complexity, performance of the product can be increasingly confirmed based on a suite of testing approaches. For example, determinants may include the marketing history of the product, safety profile, dose, and indications, among others. After an assessment of the comparative characterization data, along with a careful evaluation of properties of the product, additional testing may be warranted. This testing could include PK/PD, animal pharmacology-toxicology testing, immunogenicity, and targeted clinical safety and efficacy testing. Moving forward, the type of additional studies to be performed should be based on a risk assessment of the product and should be focused on addressing those areas of uncertainty that remain after the analytical comparison, if any.

As Dr. Charles Cooney, who chairs the Advisory Committee for Pharmaceutical Science, recently noted, "It is the incorporation of prior knowledge, innovation of new technology and new methods, and publicly available data that defines the operative space we work in." GPhA would agree—these combined factors must be incorporated into the approaches to be utilized for abbreviated approval requirements. Industry and FDA must not rely on a simple default for a full complement of testing when it is not warranted. Rather, an abbreviated approval process should select those tests that address potential concerns based on sound scientific approaches as advised by Dr. Cooney.

We would encourage FDA to carefully examine its recommendations regarding immunogenicity for generic biopharmaceuticals. During the February DIA-FDA Workshop, several participants proffered recommendations that 'follow-on' products should undergo immunogenicity testing that go well beyond the types of studies required for brand approval. We note immunogenicity considerations took a prominent position during the February workshop. GPhA urges FDA to carefully consider the scientific principles associated with immunogenicity assessments and assure that a scientifically sound approach that is not more onerous than currently required for brand products be considered when such testing is necessary.

As FDA examines the proceedings from the February Workshop, it is important for the Agency to recognize that reports from the breakout sessions represent a summation of the session dialogue. In most cases, the reports cannot be considered consensus opinions of the entire industry. Because the majority of attendees represented brand interests, it is incumbent upon FDA to carefully evaluate these reports and focus on true science and not anecdotes or unsupported hypotheticals. These diversions provide only conjecture without scientific underpinnings. Rather, the focus for FDA should be on moving toward a well-crafted industry guidance that outlines the recommendations for abbreviated data packages to support approval of generic biopharmaceuticals.

Most important, FDA has both substantial expertise and experience. With a decade of experience in assessing risk of biological products, and the potential impact of changes to products based on comparative evaluations, FDA is well positioned to provide guidance to industry and ultimately assess the abbreviated data packages that will support approval of generic biopharmaceuticals.

The next steps in realizing generic biopharmaceuticals rest largely with FDA. After two workshops that solicited input from industry, FDA has afforded stakeholders an opportunity to bring forth their respective scientific positions and views on establishing an abbreviated approval process. Additional workshops will not add new information or improve the quality of the debate, but prolong it. There is no reason to delay consumer access to affordable biopharmaceuticals when sound science supports their approval under a shortened and less costly abbreviated approval pathway. Both workshops demonstrated that there are scientific approaches that permit abbreviated data packages that will assure safety and efficacy of low to moderately complex biopharmaceuticals; more workshops are not needed to reiterate the same points.

As Acting Commissioner Crawford has stated, FDA intends to issue a background document, a position paper on follow-on proteins, and guidance on immunogenicity, with others to follow. FDA should move to issue these documents soon in order to assure that the momentum gained from the September 2004 and February 2005 workshops is maintained. Even more important, delays in moving forward with an abbreviated approval process will continue to unnecessarily deny consumers access to more affordable biopharmaceutical products.

Based on the scientific underpinnings that support establishing an abbreviated approval pathway for generic biopharmaceuticals, GPhA requests that FDA move swiftly on this national priority. We urge FDA to move forward expeditiously in completing and releasing appropriate draft guidances. GPhA believes that all of the issues have been adequately raised in the September and February forums, and that little if any new insights will be raised by continuing with public workshops. Rather, the publication of draft guidances will enable any scientific issues to be adequately addressed at that time, rather than in a continuing hypothetical discussion that will only increase the delay in defining an appropriate regulatory approval process.

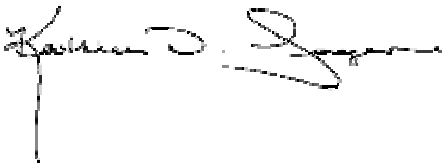
Once these drafts are published, all interested parties will have an appropriate opportunity to carefully evaluate these proposals and respond in an open and transparent manner. This will ensure that the process of defining an abbreviated approval pathway for generic biopharmaceuticals will continue without delay. It is in concrete response to draft guidances that members of the industry and FDA will be able to resolve any outstanding scientific issues. But publication of such guidance will signal to all parties the sincerity of FDA's intent to communicate a definitive process in a timely fashion.

GPhA also believes that the FDA should not delay the approval of appropriate applications filed under existing provisions of Hatch/Waxman while this process is ongoing. There already exists an appropriate approval pathway for generic versions of select, simple biopharmaceutical products. Applications based on this process must be allowed to go forward during the interim.

The American public should have access to safe, effective and affordable biopharmaceuticals. To quote Dr. Crawford, the science is here and "we have to put a system in place to deal with it."

GPhA looks forward a continued collaboration with FDA to finalize this abbreviated pathway. We look forward to the opportunity to comment on draft guidances, and to resolving outstanding issues as related to more complex biopharmaceutical products.

Sincerely,



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