

GPhA

GENERIC PHARMACEUTICAL ASSOCIATION

December 8, 2004

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
Follow-On Protein Products**

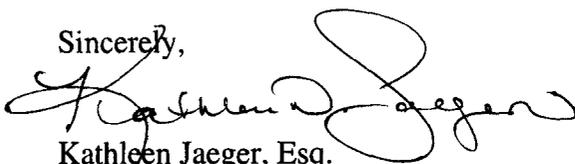
Dear Sir or Madam:

The Generic Pharmaceutical Association (GPhA) submits the enclosed comments to Docket No. 2004N-0355 Scientific Considerations Related to Developing Follow-On Protein Products.

Our comments address key questions regarding developing follow-on protein products as outlined in the Federal Register Notice dated August 16, 2004 as well as issues raised at FDA's September 14-15, 2004 Public Stakeholder Workshop.

GPhA appreciates the opportunity to comment on this important issue and applauds FDA for leading the discussion which we believe will provide a framework for an abbreviated approval process that will result in both increased access and affordability of critical biopharmaceutical products.

Sincerely,



Kathleen Jaeger, Esq.
President and CEO

2004N-0355

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**BIOPHARMACEUTICALS (“FOLLOW-ON” PROTEIN
PRODUCTS): SCIENTIFIC CONSIDERATIONS FOR AN
ABBREVIATED APPROVAL PATHWAY**

Generic Pharmaceutical Association (GPhA)
December 8, 2004

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I. BACKGROUND

For the purposes of this paper, the term “biopharmaceuticals” (so called “follow-on biologics”) are defined as biological products independently developed by manufacturers other than the brand manufacturer that are alternatives to, or interchangeable with, a brand product. Biopharmaceuticals are expected to be comparable to an approved reference product or products.¹ Based on comparisons with and demonstration of comparability to an approved reference product or products, manufacturers of biopharmaceuticals would be approved based on reduced preclinical and clinical data requirements.

Reduced preclinical and clinical requirements are supported by the Food and Drug Administration (FDA’s) approach to well-characterized biotechnology products. As part of its final rule, the FDA took the opportunity to delineate which categories of products the rule addresses. In so doing, FDA defined “well characterized” products as: “chemical entities whose identity, purity, impurities, potency and quantity can be determined and controlled.”² Such product characteristics have provided the basis for various FDA, EMEA, and ICH guidances/guidelines.³⁻⁹ These guidance/guidelines address relevant quality issues with emphasis on analytical characterization.

The Agency, as well as EMEA and the ICH Expert Working Group, recognized that available advanced analytical technologies and well-controlled processes allow different approaches to assess many aspects of product quality. Requirements of both lot release and Establishment License Applications were eliminated for these products and, in many cases, analytical characterization was used instead to establish linkage between product characteristics and safety and efficacy. Most importantly, effects of manufacturing changes and product comparability can be evaluated by quality assessments using a series of analytical tests without additional non-clinical and clinical studies as prescribed in ICH Q5E.⁶

An abbreviated approval process for biopharmaceutical products should be considered based on product comparisons and demonstration of comparability to a reference product. For draft guidance on biopharmaceutical products, the agency should address scientific approaches based on the ability to analytically characterize the product as well as other relevant scientific and medical parameters. By definition, biopharmaceutical products are not new molecular entities (NME), and therefore, pre-clinical or clinical studies are not intended to re-establish safety and clinical profiles of the products. Instead, approaches and principles as prescribed in FDA Guidance, entitled “Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products and ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process” should be extrapolated for the approval of alternative and generic biopharmaceutical products. Specifically, this guidance document reduces the regulatory burdens on manufacturers as a result of developments and improvements in production methods, process and control test methods, and test methods for product characterization. As such, analytical testing may demonstrate that a biopharmaceutical product manufactured using a new master cell bank, new manufacturing site, or manufactured with other major changes to the process need not

require preclinical animal studies or clinical studies to demonstrate safety, potency, identity, purity and quality if analytically comparable. Results of comparative studies that establish comparability of a biopharmaceutical product to the brand product should be used to determine the overall approval requirements and whether confirmatory pre-clinical and clinical studies are necessary.

Among the specified biopharmaceutical products, there are widely diversified entities in terms of their structural complexities and clinical experiences. At one end, products such as growth hormone and interferon have extensive clinical and manufacturing experience, in addition to relative simple, well-known structures. At the other end, some newly introduced monoclonal antibodies are large glycoproteins for which there may be limited market and manufacturing experiences. Given this continuum of product complexity, the Agency should take into consideration the following factors on a case-by-case basis when addressing an abbreviated approval pathway:

- Existing product manufacturing, marketing and clinical experience which can provide extensive safety and efficacy profiles, either by literature or publicly available information;
- Complexity of protein structure, for example, a small, non-glycosylated and highly purified protein, with known DNA coding sequence and amino acid sequence vs. a large, multimeric, glycosylated protein;
- Availability of structural information such as DNA sequences, amino acid sequence, secondary, and tertiary structures;
- Linkages between quality attributes and clinical activities, both safety and efficacy, such as relevant bioassay;
- Known mechanism of drug action and/or validated biomarkers; and
- Extent of clinical experience in the indicated use.

Lastly, alternative and generic access to biopharmaceutical products is of increasing importance to the health and welfare of Americans. The National Organization of Rare Diseases reports that 50 percent of all approved biopharmaceuticals on the U.S. market are intended for use in orphan conditions, with 20 percent of all marketed orphan products being biopharmaceuticals. Further, CMS reports that nearly one-third of top products purchased by Medicare are biopharmaceuticals.¹¹ Thus, the need to expedite a scientifically appropriate abbreviated approval process to provide consumers and health care providers with access to affordable biopharmaceutical products has never been more important.

II. OBJECTIVE

In submitting these comments, the Generic Pharmaceutical Association is:

- Providing a written response to the public docket established for comments on the September 14-15, 2004 Workshop on Follow-On Products,¹²
- Setting forth concepts for a scientifically sound pathway for an abbreviated approval process for “biopharmaceutical” products, and
- Addressing scientific issues raised by others and correcting common misconceptions.

GPhA is of the opinion that the scientific infrastructure exists today to support the approval of most biopharmaceutical products under an abbreviated approval pathway. And, that the time is now, to establish the requisite approval considerations for these products so that health care providers and consumers can have access to affordable biopharmaceuticals.

III. TERMINOLOGY

GPhA has used throughout this paper the term “biopharmaceuticals” in the sense that the Agency has proposed, i.e., to describe a “protein that is intended to be a similar version or copy of an already approved or licensed protein pharmaceutical product.”¹³ For the purpose of these comments, the term biopharmaceuticals consists of both alternative brand and generic products approved subject to an abbreviated pathway.

Nomenclature is a critical consideration as we move towards an abbreviated approval process for biopharmaceuticals. Terminology will play a critical factor in both patient and practitioner acceptance of these products. Both health care providers and patients alike can easily develop misconceptions regarding therapeutic agents if the terminology is confusing or misunderstood. GPhA therefore commends the agency for its proactive stance in requesting input, and its careful evaluation of the proposed terminology to avoid adopting nomenclature that could create patient confusion, or worse, misrepresentation of products approved by an abbreviated approval pathway.

Noninterchangeable Products: Biopharmaceuticals approved subject to an abbreviated process can fall within one of two classes: (1) interchangeable, or (2) noninterchangeable. GPhA maintains its position that biopharmaceutical products approved subject to an abbreviated pathway that are not deemed to be interchangeable require no unique terminology.¹² This position is based on FDA’s long standing practice for noninterchangeable NDAs as well as biopharmaceutical products that have been approved based on abbreviated data, such as, hepatitis B vaccines or influenza type B vaccine. Although many noninterchangeable products have been approved based on abbreviated data packages, the information was sufficient for FDA to make the important determination that the products were both safe and effective. This determination alone speaks for itself and no qualifying term is necessary to describe the products. In fact, creating separate nomenclature for safe and effective products that are deemed to be noninterchangeable, would suggest that such products have different quality or efficacy standards than a product that performed all of the traditional safety and efficacy studies and receive the SAME determination of safety and efficacy. In summary, FDA should

not alter its longstanding policy that noninterchangeable products supported by abbreviated data packages, which are sold as separate, and distinct products from the reference product are merely alternative brand products and are not defined using unique terminology.

Interchangeable Products: GPhA believes that it may be preferable for biopharmaceutical products that are deemed to be interchangeable to utilize unique nomenclature that denotes that the products are 'biogenerics' or 'interchangeable' products. At the present time, members of the Generic Pharmaceutical Association are evaluating potential terms that represent scientifically sound and logical nomenclature and which can be understood and embraced by consumers. GPhA believes that the critical factor in establishing the nomenclature for interchangeable products is that the term of art conveys to consumers and healthcare providers that interchangeable products provide the same therapeutic effect as their brand name counterparts. As FDA and industry considers potential terms for interchangeable biopharmaceuticals, the use of focus groups should be employed to minimize the risk of adopting a term that could create doubt or confusion to the public at large.

FDA Workshop Questions on Terminology

Question 1:

Please comment on the appropriateness of this notice's working definition of "follow-on protein" as a protein that is intended to be a similar version or copy of an already approved or licensed protein pharmaceutical product.

GPhA Response:

As discussed above, GPhA does not believe that unique terminology is required for protein products that are approved based on an abbreviated pathway and which are marketed as alternative brand products (noninterchangeable entities). For biopharmaceuticals that are deemed to be interchangeable, GPhA members are evaluating potential terminology and anticipate providing the agency with additional suggestions for its consideration. GPhA strongly believes that the terminology for generic biopharmaceuticals (i.e., interchangeable products) must convey to the public at large, confidence that the products can be safely interchanged with their brand counterparts.

Question 2:

Please comment on this notice's working definition of a "second-generation protein product" as a product similar to an already approved or licensed product but which has been deliberately modified to change one or more of the product's characteristics (e.g., to provide more favorable pharmacokinetic parameters or to decrease immunogenicity).

GPhA Response:

GPhA does not believe that unique terminology is required for biopharmaceutical products that are deliberately modified from an already approved or licensed product.

These products will not be interchangeable with the approved/licensed products and, thus, such a distinction is not warranted. For example, in many cases drug products that represent chemical or formulation modification may be 'second generation' products, however there has been no compelling reason to distinguish these products on that basis. Since any 'second generation' is deemed to be safe and effective, there is no reason to create new terminology for these products. If, however, the agency elects to adopt the proposed terminology we submit that this terminology applies equally to synthetic and bio-derived brand products.

IV. EQUIVALENCE VERSUS COMPARABILITY

The acceptance criteria for a side-by-side comparison of any two pharmaceutical products for the purpose of linking product quality attributes to safety and efficacy properties of the two should be the same for a between-manufacturer comparison as they are for a within-manufacturer comparison. The between-manufacturer comparison could arise when a competitor seeks to develop a generic version of a pioneer product or when a pioneer sells the rights to its product to a second firm or outsourcing the production operation to a contract manufacturer. A within-manufacturer comparison could arise when a pioneer seeks to change its process, formulation, manufacturing site, etc. The number and types of tests applied will generally depend on the type of product, as well as known differences in process and/or formulation, but the acceptance criteria, should, nevertheless remain the same for these two types of comparisons.

For conventional small molecule pharmaceuticals, the standards for within- and between-manufacturer comparisons are the same, and have been for about 20 years. In fact, these standards were originally developed for within-manufacturer changes for NDA products. When the Hatch-Waxman Act was passed, these same standards were then applied to link the safety and efficacy of generic products to the safety and efficacy of the corresponding reference products. The standard implemented for such conventional small molecule pharmaceutical products is that of pharmaceutical equivalence and bioequivalence which, in part, involves a rigorous and highly conservative statistical requirement.^{14 15} The extent of testing required may be reduced for small changes/differences, as illustrated by the various SUPAC guidances, but the criteria for how close two products must be in order to be considered equivalent remain constant for between- and within-manufacturer comparisons.^{16 17 18 19 20} Such a stringent requirement is utilized in order for a generic drug to be considered as therapeutic equivalence to a Reference Listed Drug without a comparative clinical study as it is not permitted in an Abbreviated New Drug Application (ANDA) under the FD&C Act.

For biopharmaceuticals the current standard for demonstrating that changes to a product's process that do not adversely effect safety, potency, purity, identity and quality is comparability, not strict pharmaceutical equivalence and bioequivalence as is the case for conventional small molecule pharmaceuticals. The current concept of comparability is described in ICH Q5E as the following:²¹

"The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change products are identical; but that they

are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product. "

Such a concept takes into consideration the unique features of protein products including complex structures to allow flexibility in comparability testing. For example, a determination of comparability can be based on a combination of analytical testing, biological assays, and, in some cases, nonclinical and clinical data. Comparability is based on the expectation that the safety and efficacy expected for the product from a modified process/formulation are similar to that from the original process/formulation. If comparability testing demonstrates appropriate similarity, the two products are treated as therapeutically interchangeable.

When a change in the process or formulation for a biopharmaceutical is implemented, a comparability assessment is executed by comparing product made by the modified process with that made by the original process or formulation. This comparison relies heavily or entirely on analytical characterization, although sometimes nonclinical, pharmacokinetic, pharmacodynamic or clinical studies may be considered on a case-by-case basis. In fact, one of the principal stated objectives of comparability studies is to reduce or eliminate the need for clinical studies if results of analytical testing are satisfactory.²¹ Comparability exercises (used in Q5E) may be executed for a wide variety of process and formulation changes, including such potentially significant ones as changing master cell banks or manufacturing sites. Successful execution of a comparability testing is the established method by which a marketed biopharmaceutical (including formulation and process) is linked to the corresponding product (including formulation and process) that was shown to be safe and effective in previous clinical trials. Process changes among biopharmaceuticals are frequent, as are the use of comparability studies to justify such changes. Comparability studies, then, are essentially benefit/risk assessments, where the benefit of limiting patient exposure in clinical trials and maintaining drug supply are weighed against the likelihood of the process/formulation change resulting in a clinically relevant change in the product's safety and efficacy.

Although not yet clearly defined in guidances, the process by which the safety and efficacy of a second manufacturer's biopharmaceutical could be linked to that of a reference product should involve the same standard of comparability assessment as for reference products when changes have been made. As envisioned by GPhA, a biopharmaceutical manufacturer would execute a comprehensive side-by-side comparative analytical characterization on the biopharmaceutical product and the reference product. If the results met appropriate standards of comparability, then the need to conduct further studies, such as preclinical, pharmacokinetic, pharmacodynamic, or clinical studies could be reduced or even eliminated. The means by which suitable comparability acceptance criteria can be developed are discussed below in the section entitled VI. CHARACTERIZATION ACCEPTANCE CRITERIA. Two competitive biopharmaceuticals (e.g., brand and generic) found to meet comparability standards in this manner ought then to be treated as if they were therapeutically interchangeable.

V. CHARACTERIZATION

Much confusion exists regarding the criteria of characterization, its capabilities and limitations, and the role it plays in an abbreviated approval pathway for biopharmaceuticals.

Three critical questions relevant to the characterization of biopharmaceuticals are:

- If two biopharmaceuticals are comparable by extensive analytical tests can we infer that the clinical safety and efficacy profile will be comparable? Can we assume that any subtle product differences are more easily detected by analytical methods than through clinical trials? (Analytical capability)
- What criteria should be applied to the characterization data to determine comparability? In other words, how close is close enough? (Criteria)
- Is it possible to have two biopharmaceuticals made with completely different processes, and yet meet comparability criteria? (Process capability)

Characterization, in the context of this discussion, is a comprehensive measurement process. However, the act of taking measurements alone does not establish comparability. Rather, these results also need to be evaluated against meaningful product criteria. How such criteria are developed is discussed in the next section, VI. CHARACTERIZATION ACCEPTANCE CRITERIA.

Absolute or Comparative Characterization

It is generally acknowledged that no “one” analytical method is currently capable of such comprehensive analysis. Instead, a collection of orthogonal analytical methods is needed to piece together a complete picture of a biopharmaceutical. Such an analysis can be accomplished in two different ways. On one hand, comprehensive analysis of a biopharmaceutical can be done for the purpose of simply describing the product without comparison to another product. This can be thought of as absolute characterization. One can conceive of absolute characterization as having sufficient data to describe the product at the atomic level. Such absolute characterization is the norm for the vast majority of small molecular pharmaceutical products, but is much less common for biopharmaceuticals. In the context of biopharmaceuticals, such an absolute characterization could include, among other things, determination of the complete three-dimensional structure of a protein at the atomic level.

On the other hand, a comprehensive analysis of a biopharmaceutical and a reference product together can constitute a comparative characterization, the objective of which would be to determine the similarity or dissimilarity of the two products. A comparative characterization need not fully elucidate all aspects of both products in absolute terms – in contrast, it need only compare the two products in all meaningful ways. Using the same biopharmaceutical example, a comparative characterization need not elucidate the complete three-dimensional structure of both proteins at the atomic level to determine

how similar they are. Instead, their similarity or dissimilarity may be compared using an array of different analytical methods that would detect any differences in the three-dimensional structures of the two proteins. High information content analytical methods (i.e., those that provide a biochemical “fingerprint”) are particularly useful for such a comparative characterization, even if the methods do not enable complete description of each product in absolute terms. This is true, because the objective of a comparative characterization is to assess comparability between the two products. Comparability of the fingerprints of the two products can, in this way, provide a high level of assurance that the two products are indeed comparable without necessarily completely elucidating either product in absolute terms.

Approved biopharmaceuticals span a broad range of complexity and heterogeneity, ranging from small, simple, homogeneous products to large, complex heterogeneous mixtures. Comparative characterization of two products may often be considerably simpler than absolute characterization of the same two products, especially in the case of more complex, heterogeneous products. For example, determining how a small homogeneous protein is folded in absolute terms at the atomic level may be accomplished using single crystal x-ray diffraction, which can be difficult, expensive, and not always successful. Verifying that the same small homogeneous protein produced by two different processes is folded in the same way can be accomplished much more easily by comparing the respective spectra using methods that are sensitive to differences in secondary and higher order structure, such as circular dichroism (CD), infrared (IR) spectra, and fluorescence spectroscopy. Nevertheless, some protein products including highly complex products have been well characterized by their manufacturers in the absolute sense. Examples include recombinant tissue plasminogen activator (rTPA), interferon beta, and filgrastim.^{22 23 24}

The distinction between absolute and comparative characterization is critical, because only comparative characterization is relevant to the determination of similarity of two biopharmaceuticals. Some firms have claimed that their biopharmaceuticals are not fully characterized. While this may be true in the *absolute* sense for some of the higher molecular weight, more heterogeneous proteins, current technology is capable of fully characterizing even such complex proteins in the *comparative* sense. Indeed, it is precisely this type of comparative characterization that brand firms employ routinely in comparability studies, even on highly complex, heterogeneous products, to detect changes relevant to safety and efficacy.

Modern Analytical Capabilities and Limitations

The power of analytical methods for characterization of proteins has increased dramatically over the past few decades. Consequently, there are many biopharmaceuticals whose original characterization for approval was not nearly as comprehensive as what would be possible using current analytical technology. This is one of the reasons that some brand manufacturers have claimed that their products have not been fully characterized. Even for these reference products, comparability protocols can and are utilized to allow for manufacturing changes.

Although current analytical methods are capable of absolute characterization of some biopharmaceuticals, complete absolute characterization of some of the more complex, heterogeneous biopharmaceuticals may be infeasible. In contrast, current analytical technology does permit complete comparative characterization of most, if not all, biopharmaceuticals.

While no one method by itself permits complete characterization of a biopharmaceutical, taken together, an appropriate suite of such tests can provide comprehensive comparative characterization of all clinically meaningful properties of a biopharmaceutical. In fact, the results of analytical characterization are often more sensitive to product changes than are clinical studies.

As with any pharmaceutical product, the critical aspects of biopharmaceutical characterization include identity, potency, safety, quality, and purity. Analytical characterization addresses all three of these critical aspects.

Perhaps the most basic aspect of identity for a biopharmaceutical is its covalent structure. Determining the complete and absolute covalent structure is now routine using appropriate combinations of methods, such as LC/MS/MS, peptide mapping, amino acid sequencing, and disulfide bond-locating methods. Largely due to the development of high resolution LC/MS/MS, virtually any difference in the covalent structures of two biopharmaceuticals, however small, can now be detected reliably. Historically, protein molecular mass was reported to only the nearest 1 or 2 kilodaltons, whereas it is now routine to report it to the nearest dalton.

A second aspect of identity for biopharmaceutical is the secondary and higher order structure. Although absolute determination of secondary and higher order structure of biopharmaceuticals is sometimes difficult, a variety of analytical methods can compare secondary and higher order structure precisely and reliably. Such methods include circular dichroism, Fourier transform infrared, fluorescence spectroscopy, immunological methods, differential liquid-liquid partitioning, HPLC retention times, etc. Application of an appropriate collection of analytical methods permits a highly reliable comparison of the respective secondary and higher order structures of the two products.

Purity assessment is typically twofold – quantitating the amount of the desired moiety as well as quantitating impurity content. Quantitating the desired moiety or moieties may be done by HPLC or other methods. Highly sensitive and selective analytical methods are routinely used for monitoring impurity content, including aggregates. Such methods include HPLC, size exclusion chromatography, polyacrylamide gel electrophoresis, capillary electrophoresis, isoelectric focusing, static and dynamic light scattering, analytical ultracentrifugation, immunological methods, etc.

The ability to chemically characterize proteins has improved substantially since the first therapeutic proteins were approved. Some proteins are so well characterized that chemical methods have replaced potency measurements as has been done with insulin, somatotropin and calcitonin.

Clearly, all critical aspects of comparative characterization are well supported by current analytical technology.

Recent claims that current analytical characterization failed to detect product changes that impacted the safety or efficacy of a product are generally attributable to one or more of the following causes:

- The use of older, less powerful analytical techniques.
- Inadequate characterization – sufficiently sensitive and selective analytical technology was available to detect the clinically meaningful change, but was not employed.
- Changes that were detected analytically, but not acted upon because they were not recognized as having a clinically meaningful impact.

Thus, most of the “characterization” problems reported historically resulted either from applying inappropriate analytical tests or interpreting the test results improperly. GPhA is not aware of any instances of a good faith and thorough application of a comprehensive suite of modern analytical methods failing to detect a significant change in a product’s safety or efficacy qualities. Quite the contrary, numerous examples have been given of manufacturing changes resulting in what could have been clinically relevant changes that were detected by analytical methods employed in comparability protocols.

FDA Workshop Questions on Characterization

Question 1

What is the capability of current analytical technology to adequately characterize protein products?

GPhA Response

Current analytical technology has the capability to perform adequate and meaningful comparative characterization for most approved biopharmaceuticals. Current analytical technology also is capable of performing adequate and meaningful absolute characterization for many Biopharmaceuticals, but this is not directly relevant to the discussion of biopharmaceuticals for the reasons set forth above.

Question 2

Are there new technologies that hold promise for helping to characterize proteins?

GPhA Response

Yes. New technologies are being developed and commercialized at a rapid pace. Of particular utility in characterization studies are high information content methods, particularly multidimensional ones, such as LC/MS/MS. Such multivariate mathematical

and statistical methods are already available, but generally underutilized in the analysis of characterization data. These methods are capable of sorting through hundreds or thousands of variables.

Question 3

What factors, including quality attributes, impurity profiles, and changes in the manufacturing process, should be considered when assessing similarity of different protein products?

GPhA Response

The factors that should be considered in the characterization process should be those that impact the identity, purity, potency and bioavailability of the product. Similarities or differences in the two manufacturing processes being compared should be considered in deciding the scope of characterization testing needed. The power of current analytical methodology, combined with modern concepts of quality management, reinforced by in-process controls and validation, allow for a high confidence level that a biopharmaceutical generic is comparable to the brand product.

Regardless of whether a protein product is a brand or a generic biopharmaceutical, it must be produced with a consistent manufacturing process that has the features necessary to ensure the identity, potency, purity, quality and safety of the final product. These features include robustness and reproducibility, validation, controls, and testing. There is a strong relationship between analytical characterization and these features of the manufacturing process. Bringing these capabilities together give confidence that the final generic biopharmaceutical product is comparable to the reference product and will remain as such.

The quantity and quality of impurities between a biopharmaceutical generic and a reference product may be different. They may have different process related impurities because they are made by different manufacturing processes. However, two products made by different processes may have similar product related variants or impurities. It may not be relevant that process related impurities are different considering that today's recombinant proteins are highly purified and generally impurities are less than 3 % and often less than 1 %. One should consider that process related impurities do not cause adverse events, and generally adverse events are caused by the inherent pharmacology of the protein. When impurities are this low it may not matter if they are different from impurities of the originator protein.

Question 4

Is it possible to accurately predict safety and efficacy from analytical studies?

GPhA Response

Predicting safety and efficacy for a new reference protein based solely on analytical studies is difficult. This is not the question at hand since the brand product has already established safety and efficacy through the animal and clinical studies. A more pertinent question is whether the impact of composition differences between two products on safety and efficacy can be anticipated by analytical studies. The answer to this latter question is clearly yes. Such predictions are the cornerstone for comparability studies, and have been in widespread use for years.

VI. CHARACTERIZATION ACCEPTANCE CRITERIA

One key objective of comparative characterization is to provide assurance that two products are sufficiently similar analytically that their clinical effect will be comparable. Given this knowledge, animal and clinical testing can be significantly reduced or eliminated. The greater the extent of characterization and the closer the match between a test product and the corresponding reference product, the greater the assurance of comparable clinical effect. Therefore, the scope of any in-vitro and in-vivo programs should be inversely related to extent of characterization and closeness of the match between the test and reference products.

Several factors need to be considered in fashioning sound and practical acceptance criteria for analytical characterization data, including criteria used in comparability protocols, observed reference product variability, historical changes, and drift in the reference product. Because each product has its own background, properties, risks, etc., it may be necessary to individualize acceptance criteria for each product.

Observed variability in the reference product

The inherent variability in biopharmaceuticals means that the target product is not defined by a single value for each analytical parameter (i.e., a point corresponding to a single lot), but rather a spread of values spanned by multiple lots of the reference product. Constructing meaningful comparability criteria is critically dependent upon understanding the lot-to-lot variability of the reference product. Therefore, measuring the lot-to-lot variability of the reference product for a baseline assessment is one of the principal objectives for a biopharmaceutical firm to achieve in its characterization studies.

Variability in the reference product should play a role in determining acceptance criteria width, i.e., the goalposts – just as the Advisory Committee for Pharmaceutical Sciences recommended for bioequivalence standards for highly variable drugs in April 2004. In that meeting, the Advisory Committee voted in favor of adjusting the width of the bioequivalence confidence interval criteria in accordance with the observed variability of the reference product (reference scaling) for highly variable drugs.

Another factor that should be taken into account is that, for a given product, some tests will show greater lot-to-lot variability than others, largely because the product actually

varies more in some aspects than in others. Therefore, even for a given product, acceptance criteria width may need to vary by analytical test.

Clinically tested range of variation and product changes

The range of variation in the reference product that was actually used in the reference products clinical studies (i.e., clinical trial batches) can be thought of as defining a set of boundaries within which the reference product has been shown directly to be safe and efficacious. These boundaries can be thought of in terms of composition (i.e., the range of compositions tested clinically), or processing/formulation parameters (i.e., the range of any variation in process and/or formulation among the lots tested clinically). It is common for reference products to employ processes, compositions, and/or formulations for marketed products that are outside the boundaries of what was actually tested clinically. These extrapolations beyond the clinically tested region result from application of changes justified by comparability studies.

Available data linking analytical test parameters and clinical effects

It is recognized that *in vivo* – *in vitro* correlations typically do not exist. However, any such *in vivo* – *in vitro* correlation that is already publicly available should be taken into account in fashioning comparability acceptance criteria. If such *in vivo* – *in vitro* correlation data are not publicly available, the Agency should not require biopharmaceutical firms to generate this information, as this is generally not required for brand firms seeking process/formulation changes. Nevertheless, the use of existing information could be useful in fashioning suitable acceptance criteria.

Interchangeability versus approvability

Another key factor in constructing appropriate acceptance criteria for analytical characterization is whether a conclusion of interchangeability is desired, or only a conclusion of approvability. Obviously, the criteria to conclude that the test product is interchangeable with the reference product could be narrower than criteria to conclude that the test product is comparable to the reference product and is approvable (but not necessarily interchangeable).

The final conclusion of interchangeability or approvability needs to be made in view of any preclinical, pharmacokinetic, pharmacodynamic, and clinical results that are generated. Nevertheless, the characterization acceptance criteria should be designed with a view toward whether a determination of interchangeability or approvability is sought. If the comparative characterization data leave uncertainty about the conclusion of interchangeability or approvability, the scope of any preclinical, pharmacokinetic, pharmacodynamic, or clinical testing should be adjusted accordingly to resolve this uncertainty.

Biological activity assays

Although it may not be possible to precisely replicate each of the brand product's test methods, comprehensive testing can assess the same underlying biological characteristics

of a product in other ways – i.e., the collection of tests done by the biopharmaceutical product manufacturer in the course of comprehensive comparative characterization may assess the same battery of biological properties that the collection of tests done by the brand assesses. This is particularly true of biological activity assays, for which a biopharmaceutical product manufacturer may not have access to the test methods, or cell lines used in testing the reference product. In such cases, biopharmaceutical manufacturers can develop similar biological activity assays, or employ some combination of tests that yield the same information as the reference's biological activity assay(s). As long as the cumulative results of all of the tests proposed demonstrate comparability, the identity, purity, potency, quality, and safety of the biopharmaceutical product can be assured. This does not imply that an understanding of structure-function relationships should be required for approval. In fact, structure-function relationships are often unknown even to reference product manufacturers.

Because of the improvement in physicochemical assays and the inherent variability of most bioassays characterization methods have shifted from being biologically based toward being chemically based. Stability assays for biopharmaceuticals now rely predominantly on chemically based assays rather than biological activity assays. Dosing of biopharmaceuticals has changed over the past 15 years from units to mass because of greater reliance on chemically based assays.

FDA Workshop Question on Preclinical and Clinical Issues

Question:

When and how would it be appropriate to streamline or eliminate certain animal or human studies during development of a biopharmaceutical product?

GPhA Response:

The same principles and criteria currently in use for the execution of comparability protocols for process changes to a reference product should be applied to the comparative characterization of a biopharmaceutical product. The principal objective of comparability protocols is to reduce or eliminate the need for human clinical studies. As stated above, the following factors should be among those considered in developing acceptance criteria and determining the extent of preclinical, pharmacokinetic, pharmacodynamic, or human clinical studies:

- Extent of characterization
- Comparability of biopharmaceutical product to reference product
- Observed variability in the reference product
- Available data linking analytical test parameters and clinical effects

FDA Workshop Questions on Potency and Surrogates for Efficacy and Safety

Question 1:

What factors should be considered regarding bioactivity and potency assays used for comparing two products?

GPhA Response:

Over time the emphasis in characterization of biopharmaceuticals has shifted from bioassays to chemical assays because of the improvement in the chemical assays and the inherent variability of most bioassays. Even though a biopharmaceutical manufacturer may not have access to the testing methodology used to test the reference product, it can still develop comparable methods that yield equivalent information.

Question 2:

What is the role of in vitro and in vivo assays for use as surrogates in establishing safety and efficacy?

GPhA Response:

In the context of developing a biopharmaceutical product, establishing safety and efficacy *de novo* is generally not the objective. Instead, the biopharmaceutical product would ordinarily be compared to the reference product. Therefore, the whole array of studies performed during comparability testing, including analytical characterization tests, preclinical studies (if any), pharmacokinetic studies (if any), pharmacodynamic studies (if any), and clinical studies (if any) should collectively be sufficient to determine whether the results from the biopharmaceutical product are sufficiently close to those from the reference product to conclude that the two are comparable and, therefore, interchangeable. In this setting, *in vitro* and *in vivo* assays can help to support the conclusion of safety and efficacy for the biopharmaceutical product. The extent of this support needs to be determined on a case by case basis taking into account the factors cited above in the response to the question on preclinical and clinical issues.

VII. MANUFACTURING

Because of the manner in which brand's formulation and process changes are supported, the yardstick by which a change is judged is, by definition, not whether the *process* is the same as the original process. But, rather, whether the magnitude and acceptability of the changes *observed* as a result of that change, as assessed by characterization studies and possibly preclinical, pharmacokinetic, pharmacodynamic, and/or clinical studies. The importance of the process is to ensure that the resultant product consistently meets these requirements. The process is, therefore, not the end in and of itself, but rather a means to achieve the end. The objective is really a final product (composition) that is approvable. Any reproducible process that yields a final product that matches the desired composition (based on comparability to the reference product) should, therefore, be equally acceptable. The power of current analytical methodology, combined with modern

concepts of quality management, reinforced by in-process controls and validation, allow for a high confidence level that a biopharmaceutical generic is comparable to the reference product.

Regardless if a biotech product is either a reference or biopharmaceutical product, certain features of the manufacturing process need to be maintained in order to insure the identity, potency, purity, quality and safety of the final product. These features include robustness and reproducibility, validation, controls, and testing. There is a strong relationship between analytical characterization and these features of the manufacturing process. Bringing these capabilities together give greater confidence that the final product produced by a biopharmaceutical generic manufacturer is comparable to the brand product.

The manufacturing process for a biopharmaceutical product may be different than the manufacturing process for the comparable reference product. Manufacturing procedures and testing methods employed by biopharmaceutical product manufacturers will likely be more advanced than the reference product as state-of-the-art procedures and methods used today are more advanced than those used decade(s) ago when the reference product was approved. Therefore, the manufacturing process, test methods, and specifications for a biopharmaceutical product must be evaluated separately from the brand product. Biopharmaceutical product manufacturers should submit a full Chemistry, Manufacturing and Controls (CMC) section to their application to insure that FDA has the data and information to determine that the drug substance and drug product is safe, pure, potent and of high quality. The CMC section should include full analytical characterization, a description of the manufacturing process and test methods, and stability data. Analytical characterization should include a direct comparison to the brand product to demonstrate comparability.

FDA Workshop Questions on Manufacturing Issues

Question 1:

What aspects of the manufacturing process determine the characteristics of a protein product whether produced through biotechnology or derived from natural sources?

GPhA Response:

Specific aspects of the manufacturing process do not determine the characteristics of a protein product. The biopharmaceutical product is developed to be comparable to the biotechnology-derived reference product. An analytical comparability exercise should be conducted to demonstrate comparability of the biopharmaceutical product to the reference product.

Question 2:

What parts of the manufacturing process should the Agency focus on when assessing similarity between products?

GPhA Response:

Specific parts of the manufacturing process do not determine the characteristics of a protein product. The biopharmaceutical product is developed to be comparable to the biotechnology-derived reference product. An analytical comparability exercise should be conducted to demonstrate comparability of the biopharmaceutical product to the reference product.

VIII. PRECLINICAL STUDIES

Preclinical animal studies are typically not necessary. For virtually all biopharmaceuticals on the market, the product will not be endogenous to a species that might be suitable for use as a preclinical model. Consequently, long-term use in such an animal model is likely to be limited by the development of antibodies toward the product.

In any case, the need to conduct preclinical animal studies to support the development of biopharmaceutical product will generally be dictated by the questions that remain unanswered by the analytical characterization studies. Just as for analytical characterization studies, the extent of any preclinical studies, and appropriate acceptance criteria for such studies should be based on the relevance of the studies to the safety and efficacy of the product.

IX. PHARMACOKINETIC/PHARMACODYNAMIC STUDIES

The following factors could potentially affect the pharmacokinetic properties of protein products:

- Active molecule(s), including primary and higher order structure
- Dosage form
- Concentration
- Formulation
- Delivery system/route of administration

Problems in the pharmacokinetics of biopharmaceuticals have arisen where one or more of these parameters are different: the molecules are significantly different (e.g., different glycoforms or different PEGylation), formulations are significantly different, or route/method of administration is different (standard syringe + needle vs. pen). Therefore, if there were an acceptable match for all of these parameters, performing a PK study on a biopharmaceutical administered as a solution would generally be superfluous. However, if there were substantial differences for some of these parameters, a PK study could be important. A good example of this would be if the test and reference products had substantially different glycosylation or PEGylation patterns, but were otherwise comparable. In this example, the molecules in the test product would be somewhat

different from those in the reference product, and the impact of the differences in composition would generally not be predictable from analytical data alone. For those few biopharmaceuticals that are not administered as solutions, conducting pharmacokinetic studies may be important, unless reliable *in vivo-in vitro* correlation data were available to support the comparative characterization. In any case, the same principles used to determine whether a change in a reference product necessitates PK/PD studies should be applied to the determination of whether a biopharmaceutical product needed PK/PD studies. If there are uncertainties about the effect of differences in composition detected during the execution of comparability, such uncertainties are often resolved in practice, by running PK studies (animal or human) or PD studies. If doubts still remain after these PK or PD studies are completed, there still may be a need to conduct additional clinical studies.

One of the issues raised at the September Workshop was that the half-lives for the various approved products differ substantially from less than an hour to about 17 hours. The range of terminal elimination half-lives reported in the package inserts of nine approved somatotropin reference products (Nutropin, Nutropin Depot, Nutropin AQ, Humatrope, Norditropin, Gentropin, Tev-Tropin, Saizen and Zorbtive) ranges from 0.33 hours to 0.6 hours when each active ingredient is administered via the intravenous route in immediate-release formulations. This range of variation is small and reflects inter-individual variability in half-life, differences in study design, and other factors that influence cross-study comparisons. When somatotropin is administered subcutaneously or intramuscularly, the rate at which it is absorbed from the injection site into the systemic circulation is much slower than the rate at which the drug molecules are cleared from the systemic circulation resulting in a pharmacokinetic condition known as flip-flop. A number of small molecule drugs exhibit flip-flop pharmacokinetics, especially when administered as controlled-release dosage forms. When a drug exhibits flip-flop pharmacokinetics, its apparent elimination rate is determined by the absorption rate, not the rate at which the drug molecules are actually eliminated from the bloodstream. This is precisely the case with somatotropin products on the market today. All exhibit comparable true elimination half-lives, which are significantly less than one hour. The wide range of apparent elimination half-lives following subcutaneous or intramuscular injection simply reflects the differences at which each product is absorbed from the injection site largely because of formulation differences. Hence, several of the products bear the following statement in their package inserts: "The longer half-life observed after subcutaneous or intramuscular administration is due to slow absorption from the injection site."

X. CLINICAL STUDIES

One of the key aspects of an abbreviated approval process for biopharmaceuticals will be the scientifically rigorous determination of whether a limited clinical study will be required. This decision is important for two reasons. First, clinical studies should be required only when other comparative data is inadequate. In these cases, the studies should be focused on addressing those concerns not answered by other comparability data. Second, requiring limited clinical studies for only those products for which it is necessary will speed access to biopharmaceuticals. Among the key socioeconomic

aspects of bringing true affordability to these important therapeutic agents, along with increased access for patients, will be a rational, scientifically sound decision process for determining if clinical studies are necessary, and if so, a critical assessment on the study design focused on addressing the essential information to support approval of the product. The need for access to biopharmaceuticals continues to grow rapidly and provide life-saving treatment to patients. Additionally, as stated in the BACKGROUND section, the need for access and affordability of biopharmaceuticals is critical for purchasers of these products.

As described in earlier sections, comparative analytical characterization of the reference and biopharmaceutical product will provide a foundation for determining whether a clinical study is necessary. If a clinical study is warranted, this comparative data will help determine the study parameters based on the level of characterization that can be assured. The sensitivity of analytical techniques in being able to detect subtle product differences is far superior to the ability of clinical trials to detect product differences. Therefore, detailed comparative analytical characterization should serve as a baseline for clinical study decisions.

The range of variation in the reference product that was actually used in the reference clinical studies (i.e., clinical trial batches) can be thought of as defining a set of boundaries within which the reference product has been shown directly to be safe and efficacious. These boundaries can be thought of in terms of composition (i.e., the range of compositions tested clinically), analytical test results (i.e., the range of analytical test results seen from lots tested clinically), or processing /formulation parameters (i.e., the range of any variation in process and/or formulation among the lots tested clinically). It is common for brand biopharmaceuticals to employ processes, compositions, and/or formulations for marketed products that are outside the boundaries of what was actually tested clinically.

Over the last 2 decades, FDA and industry scientists have accumulated significant experience with a variety of classes of biopharmaceuticals. In part, this experience has provided substantial guidance to industry regarding risk assessment and determining if clinical studies are required when changes are made to innovator products. These changes cover a wide variety of alterations to biopharmaceuticals including changes to process, cell banks, site changes, scale-up, among others. When these changes occur, FDA carefully assesses whether the prechange and postchange comparative data, combined with information regarding the use, dose, toxicity, etc., of the product provides a sufficiently robust risk analysis to permit implementation of the proposed change(s) without performing clinical studies. In many ways recombinant products, which are typically highly purified and often defined by chemical properties particularly, lend themselves to characterization alone. However, if studies are deemed necessary, the clinical study plan should be sharply focused to provide information bridging information to address concerns not completely answered by comparative analytical information.

The Agency has considerable expertise in assessing critical factors to assure the safety and efficacy of biopharmaceutical products. FDA has utilized its experience in making

determinations of comparability since the 'comparability' guidance was published in 1996. Further, FDA, along with other international regulatory agencies and industry representatives used this collective experience to generate a decision pathway for determining the necessary data required for changes to biopharmaceutical products. This collective body of experience was put forth in the ICH comparability guidance. As pointed out in this guidance pre-change and post-change data are used to determine whether clinical studies are necessary. In most cases, clinical studies are not deemed to be necessary based on comparative characterization data. Likewise, the same approach comparing relevant quality attributes of the innovator and proposed products may be used to determine comparability. If the innovator and proposed products are sufficiently comparable no clinical testing would be required. Just as outlined in the ICH approach, more relevant information becomes available as experience is gained with the product. Additionally, improved analytical capabilities emerge over time. Products found to be appropriately similar, along with a body of knowledge that helps ensure that the differences have no impact on safety or efficacy, may forego the need for clinical trials. When analytical capabilities may not be able to precisely evaluate all quality attributes, an abbreviated clinical program may be considered. Only after a comprehensive evaluation of the comparative data can an informed determination be made in regard to whether bridging clinical studies are necessary.

In addition to the comparative analytical information available to industry and FDA, there is also considerable marketing experience available to FDA, industry and the healthcare community. This experience helps develop a more complete understanding a product's clinical performance.

In any case a scientifically sound approach that provides the requisite data should be employed. A well-designed and focused clinical approach can typically confirm with relatively small patient numbers that the new biogeneric has the same pharmacology as the innovator.

In summary, it is important for FDA and industry to carefully evaluate a paradigm for abbreviated clinical testing using its historical understanding of the issues. Analytical characterization provides the underpinning to the decision on whether a clinical study is needed. We also must recognize that analytical comparability provides a powerful tool for developing comparative information regarding the potential impact when changes are observed between the reference and proposed biopharmaceutical product. The question now relates to the sufficiency of clinical data to support approval requiring clinical trials. In other words, the scope, breath and magnitude of the requisite clinical program parameters that should depend on scientific criteria rather than requirements that provide a 'comfort level' but are not scientifically sound. Knowledge of the product and the potential impact of the changes on patient safety and efficacy should guide scientific decisions. We also must recognize that clinical trials are less likely to detect product differences than analytical comparisons. Finally, given the body of knowledge that may be provided on a potential biopharmaceutical, clinical studies may typically utilize a smaller patient population (and not to detect differences) and should certainly not exceed the size of the study population used by the reference product manufacturer in those infrequent cases for which a sizable study is merited.

XI. IMMUNOGENICITY

One of the major issues in the discussions on biopharmaceutical products is whether concerns about immunogenicity could be a hurdle in the development of these products. This issue is relevant for all reference products and is not a unique issue for biopharmaceutical products. The presence of antibodies is not always harmful. Too often immunogenicity is incorrectly associated with something that is always detrimental. However, we know that many therapeutic proteins generate antibodies with no clinical consequence.

The presence of antibodies should not always be minimized and there are cases where antibodies with clinical consequences are a concern. For example, antibodies that affect the pharmacokinetics of the protein, antibodies that diminish therapeutic efficacy, and perhaps the most serious example, are antibodies that cross-react with endogenous protein. In these specific cases immunogenicity is a valid issue. Hypersensitivity like reactions have been observed after administration of some brand protein therapeutics. It is not known whether these are true anaphylactic reactions to the protein. However, these incidences are rare and there is no analytical, preclinical or clinical predictor of hypersensitivity reactions. Because these reactions are rare it is unlikely that clinical trials would be useful in addressing whether a biopharmaceutical product was different from the reference product in the induction of hypersensitivity. It is important to recognize that hypersensitivity reactions are not unique to proteins and there are a number of drugs that cause hypersensitivity reactions such as those used in radiological imaging and antibiotics. Drug products, which are known to induce hypersensitivity reactions in some patients, have been approved with no requirement for immunogenicity testing.

Likewise, the generation of antibodies to a protein should not always be an issue. Many antibodies to therapeutic proteins are transient and most patients with antibodies to the protein continue on therapy with no clinical consequences.

Another issue to be addressed is whether immunogenicity concerns can be addressed through analytical testing prior to approval of biopharmaceutical product. One might consider taking a risk management approach in which resources are focused on assessing product factors with the greatest risk of immunogenicity. Based on more than 20 years of clinical use of hundreds of therapeutic proteins we know that aggregation is the main product factor associated with immunogenicity.^{25 26} For example, aggregates of interferon alfa-2a and human serum albumin were shown to be the cause of immunogenicity for that product. When the aggregation problem was resolved the immunogenicity of IFN alfa-2a was decreased.²⁷ While there may be other factors with a possible association with immunogenicity such as novel epitopes, impurities other than aggregation, glycosylation changes, oxidation, etc., these actually poses a very minimal risk. In fact, many of these factors, which are often cited as a possible cause of immunogenicity, are merely theoretical risk factors and have never been demonstrated to be actually associated with immunogenicity.

Since aggregates are the primary product factor associated with immunogenicity analytical testing of biopharmaceutical products for aggregation could minimize the

potential for immunogenicity. Today there is improved methodology available to measure aggregates such as light scattering, size exclusion chromatography, etc. Often, techniques to adequately measure aggregation did not exist at the time that the reference protein was approved and even today aggregation is often not measured as part of product release testing. Aggregates should be measured as part of drug product characterization, on stability, and after reconstitution if it is a lyophilized product. Many protein manufacturers use the USP specification for particulates without the acknowledgment that this was developed for typical drugs and may not be appropriate for proteins. A different specification for proteins may be necessary that takes into account the distribution and size range of particulates due to protein-protein interactions. Measurement of aggregates as a way to minimize immunogenicity is not necessarily specific to biopharmaceutical products and this concept would apply to all therapeutic proteins, including brand products. Immunogenicity of reference protein products and other new therapeutic proteins could be minimized if aggregation is monitored systematically.

Another question in this discussion is whether immunogenicity concerns can be addressed through clinical trials prior to approval of a biopharmaceutical product. Is it realistic to have a thorough understanding of immunogenicity and the clinical consequences prior to approval? The answer is probably not, but this is true for a reference protein product as well as a biopharmaceutical product. Since the incidence of antibody development does not occur in all patients and can sometimes be rare, a complete understanding of immunogenicity and its possible consequences is not usually possible until there is significantly greater patient exposure after a product has been approved. It has been suggested that the more information known about the chemistry and biology of the biopharmaceutical product the less clinical data should be required. A corollary to this might be that if extensive analytical tests demonstrate comparability between the biopharmaceutical product and the reference the chance for increased immunogenicity is minimized. If the biopharmaceutical product is comparable to the reference in all physical and chemical attributes there would be a negligible chance of increased immunogenicity. Analytical testing, beyond routine product release testing, is generally warranted and it should be emphasized that analytical assays need to be updated periodically to be assured that any product differences, whether from manufacturing changes or in a biopharmaceutical product, would be able to be detected by the best analytical techniques.

The utility of small clinical studies to assess immunogenicity needs to be seriously questioned. The limitations of small clinical comparator studies in being able to detect true differences between two products with regards to immunogenicity needs to be recognized. If extensive analytical testing has demonstrated that the biopharmaceutical product is comparable to the reference then any potential differences between the two would be very subtle. If one considers the expected differences between the two products, the size of the clinical trial necessary to demonstrate true differences in immunogenicity due to subtle product differences would be huge and may not be practical prior to approval. Clinical trials done solely to evaluate differences in immunogenicity in a limited patient population would not be scientifically valid and therefore may be of limited utility. This is to be distinguished from the assessment of antibodies to therapeutic

proteins as part of clinical development. A clinical trial should be designed to answer a sound scientific question and the assessment of immunogenicity to the therapeutic protein should be a part of the clinical trial. A complete understanding of immunogenicity and the clinical consequences may not be possible until post approval. This is true for any therapeutic protein and is not a unique issue for biopharmaceutical products. The answer to addressing immunogenicity may lie in post marketing surveillance where efficacy and adverse events could be correlated with the presence of antibodies.

In conclusion, immunogenicity should be a concern only when there are clinical consequences and one should recognize that not all immunogenicity is harmful. Immunogenicity can be minimized by focusing on analytical testing of product factors that are most associated with immunogenicity such as aggregates. The more information that is known about the chemistry and biology of the biopharmaceutical products and its comparability to the reference protein, the more that differences in potential immunogenicity would be minimized. Small clinical comparator trials may have limitations in detecting immunogenicity differences between a reference product and a biopharmaceutical product and these concerns may be better addressed in post marketing surveillance. Immunogenicity concerns can be adequately addressed for biopharmaceutical products and should not be a hurdle in their development.

FDA Workshop Questions on Immunogenicity

Question 1:

How, and to what extent, should immunogenicity be evaluated for a biopharmaceutical product?

GPhA Response:

If a biopharmaceutical is found, in a comprehensive analytical characterization study, to compare favorably with the reference product, there should be no need to conduct immunogenicity testing. Similarly, if the biopharmaceutical product is found to have lower levels of impurities, aggregates, or other objectionable characteristics than the reference product, then no immunogenicity studies should be required.

Question 2:

Under what circumstances should comparative immunogenicity studies be conducted?

GPhA Response:

The value of comparative immunogenicity studies has not been shown. For immunogenic events that occur with low frequency, comparative immunogenicity studies are statistically infeasible and may very well exceed the number of treatment-naive patients available for enrollment. Even for immunogenic events that occur with relatively high frequency (e.g., formation of non-neutralizing antibodies for some products) the value of comparative immunogenicity studies is questionable and, therefore, such studies may be unethical because they would constitute unnecessary human experimentation.

XII. PRECEDENTS

For biopharmaceuticals, some precedents for an abbreviated approval process as well as a conclusion of therapeutic equivalence/interchangeability have already been established by the agency. For example abbreviated new drug applications (ANDAs) have been approved for protamine sulfate, calcitonin, and corticotropin products. All three of these ANDA products bear an "AP" rating in the Orange Book, signifying therapeutic equivalence and interchangeability. Another biopharmaceutical, chorionic gonadotropin, while approved as an NDA, bears a similar "AP" therapeutic equivalence rating.

Additionally, for the later somatropin products that were approved, the size of the clinical studies required was less than for the first somatropin product approved, which is tantamount to an abbreviated approval process.

There are several biopharmaceuticals for which FDA has informally deemed competing products to be equivalent or indistinguishable. For example, all of the approved somatropin products have labeling statements indicating that they are equivalent to endogenous human growth hormone. Similarly, the package inserts for follitropin alfa and follitropin beta contain statements indicating that these two products are "indistinguishable". In fact, the FDA even commented that the use of the terms alfa and beta should not be interpreted as signifying that the two products are different. While these labeling statements do not carry the weight of an "A" rating, these examples do clearly indicate that the concept of equivalence or interchangeability is both possible and reasonable for biopharmaceuticals.

¹ For purposes of this submission, 'reference' product means the entity that serves as the product that a follow-on product uses in comparison. In most cases, this 'reference' product will be the innovator product.

² 21 CFR 600 and 601: Elimination of Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products

³ ICH Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products, 1995.

⁴ Q6B: Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, 1999.

⁵ The Common Technological Document For The Registration OF Pharmaceuticals For Human Use: Quality – M4Q, 2002.

⁶ QSE: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process, Step 2, 2003.

⁷ FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products.

⁸ Guidance for Industry: For The Submissions of Chemistry, Manufacturing, and Controls Information For A Therapeutic Recombinant DNA Derived Product Or A Monoclonal Antibody Product For In Vivo Use, 1996.

⁹ Guidance For Industry: Changes to an Approved Application for specified Biotechnology and Specified Synthetic Biological Products, 1997.

¹⁰ Exploring the Pathway to Generic Biologics: Are Therapeutically Equivalent Biologics Feasible and Desirable? National Organization for Rare Diseases, Conference, March 18, 2003.

¹¹ CMS Updates 2005 Part B Payment Rates: Gemzar ASP Increases by 2.3%; Pink Sheet, Nov. 8, 2004.

¹² Scientific Consideration Related to Developing Follow-On Protein Products – Public Workshop, September 14-15, 2004.

¹³ 69 Fed. Reg. 50386, August, 16, 2004, Scientific Considerations Related to Developing Follow-On Protein Products.

¹⁴ Approved Drug Products with Therapeutic Equivalence Determination, 24th Edition, p. ix-x.

¹⁵ Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, March 2003.

¹⁶ Guidance for Industry: Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation, Center for Drug Evaluation and Research (CDER), November 1995.

¹⁷ Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Docuemntation, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), September 1997.

¹⁸ Guidance for Industry: Nonsterile Semisolid Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation, U.S. Department of Health and Human Services, Food and Drug administration, Center for Drug Evaluation and Research (CDER), May 1997.

¹⁹ Guidance for Industry: SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms Manufacturing Equipment Addendum, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), January 1999.

²⁰ Guidance for Industry: SUPAC-SS: Nonsterile Semisolid Dosage Forms Manufacturing Equipment Addendum (DRAFT GUIDANCE), U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), December 1998.

²¹ ICH Draft Consensus Guideline: Comparability of Biotechnology Biological Products subject to changes in Their Manufacturing Process, Q5E.

²² Lin, L. Betaseron. *Dev Biol Stand* 96, 97-104 (1998).

²³ O'Connor, J. V. rtPA is a well-characterized protein. *Dev Biol Stand* 96, 113-21 (1998).

²⁴ Herman, A. C., Boone, T. C. & Lu, H. S. Characterization, formulation, and stability of Neupogen (Filgrastim), a recombinant human granulocyte-colony stimulating factor. *Pharm Biotechnol* 9, 303-28 (1996).

²⁵ Hermeling S, Crommelin DJ, Schellekens H, Jiskoot W. Structure-Immunogenicity Relationship of Therapeutic Proteins, *Pharm Res.* 2004 June;21(6): 897-903.

²⁶ Cleland JL, Powell MF, Shire SJ. The Development of Stable Protein Formulations: A Close Look At Protein Aggregation, Deamidation, And Oxidation. *Critical Review Therapeutic Drug Carrier Syst.* 1993; 10(4) 307-77.

²⁷ Hochuli E. Interferon Immunogenicity: Technical Evaluation Of Interferon-Alpha 2a. *J Interferon Cytokine Res.* 1997 Jul; 17 Suppl 1: S15-21.