

December 30, 2010

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

Docket No. FDA-2010-N-0477

Dear Sir/Madam:

Thank you for the opportunity to provide the Generic Pharmaceutical Association's point of view on the implementation of the new abbreviated biogeneric pathway created in the Biologics Price Competition and Innovation Act of 2009.

GPhA supports the FDA assessment, contained in the Federal Register¹ notice announcing the public meeting and the opening of this docket, that the objectives of the BPCI Act are conceptually similar to those of the "Hatch-Waxman Act", which enabled the approval of generic drugs in 1984, and made cost-effective medicines available to many more patients. Further, GPhA supports the interpretation of the BPCI Act in alignment with FDA's longstanding policy of permitting appropriate reliance on what is already known about a drug, to save both time and resources, and avoid unnecessary and unethical duplication of human or animal testing. The FDA intentions as described in the meeting notice, especially access and public health (recognizing that access is an unmet medical need), alongside the Agency's expertise and experience with biologics make the FDA eminently qualified to license biogenerics immediately.

The legislation was enacted March 23rd, 2010, and the key next step is the immediate implementation of BPCI by FDA, using its new authority to approve biogeneric as well as interchangeable biogeneric products, such that these important products reach patients as soon as possible. Sponsors need to know they will have predictable and abbreviated data burdens for biogeneric applications, and this means reliance to the full extent scientifically reasonable on prior knowledge. The lack of biogeneric applications to date, and only a modest number of meetings with sponsors interested in the 351(k) pathway already suggests that the FDA may not be encouraging biogeneric applications to the extent that our members would have hoped. We would note that GPhA is confident, given FDA's many years of experience leading the world on the licensure of originator biopharmaceuticals, that the application of consistent regulatory standards will make these biogenerics as safe, pure and potent as originator biologics. This still allows

¹ Federal register notice Food and Drug Administration [Docket No. FDA-2010-N-0477] Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing; Request for Comments. Available at: <http://edocket.access.gpo.gov/2010/pdf/2010-24853.pdf> (accessed 1Dec10)

flexibility as to biogeneric data sets and any given biogeneric sponsor's scientific justifications for their approaches, just as is the case today for innovator biologics. Data is always case by case, but standards can be consistent.

GPhA members include the leaders in the development and marketing of high quality, safe and effective biogenerics in countries outside of the US. They market biogeneric products in the highly regulated markets of the EU, Japan and Australia. Further, our membership has played a key role in assisting the health authorities of these countries implement biogeneric pathways and are currently interacting with foreign authorities on the development of more complex biogeneric products such as monoclonal antibodies (MAbs). GPhA's response to the docket draws on our members' extensive experience with the scientific development, international registration and post-marketing pharmacovigilance of biogeneric products.

An ethical and science-driven pathway for all biologics irrespective of sponsor:

GPhA looks forward to FDA ensuring that the pathway requirements for biogenerics do not require the unnecessary repetition of studies – be they analytical, preclinical or clinical. They should certainly not exceed those of originator biopharmaceuticals. That the biogeneric pathway is indeed abbreviated will be critical to its use, and hence to the success of the pathway in ensuring greater access to safe, pure, potent, high quality biogenerics once patents and exclusivity expire. GPhA has confidence in FDA leadership, and in the Agencies ability to learn from progress already made with biogenerics in other jurisdictions. We believe that the FDA can and indeed should take the best ideas and use their new authority to implement the biogenerics and interchangeable biogenerics pathways rapidly and to the full extent expected of new law. Indeed we heard many of our biopharma colleagues give credit to the processes and procedures used in other jurisdictions, especially the European Union (EU). We would suggest there is little value in repeating those efforts, for instance as the same literal series of guidelines. But to harmonize efforts from a shared collective experience in order to move ahead more expeditiously in the US does make sense. And to date the experience with biogenerics in the highly regulated markets is very positive, with no suggestions of any unusual or unexpected adverse outcomes in the marketed biogenerics.

The US has led the world in originator biologic approvals, especially but not only biotechnology-based products, and therefore the FDA already has extensive experience. Since, by definition a biogeneric will only be developed relative to a previously approved 351(a) licensed product, the FDA prior experience is necessarily relevant. The previously licensed originator biotech products will provide, in all likelihood, further experience from subsequent regulatory review of manufacturing changes, and it will be this collective history, along with at least 12 years of post-marketing clinical experience that will provide the basis for the biogeneric development by the subsequent sponsor and the FDA review. No access to the dossier of the innovator is needed, nor sought, but the very fact that the FDA has previously licensed a highly similar product is evidence that the FDA already has all the expertise/experience necessary to review biogenerics to these same products.

GPhA goal is to both support FDA and to support the objectives of BPCI very explicitly. We have great confidence in FDA's ability to use their new authority in reviewing and licensing high quality, safe, pure and potent biogenerics and thereby facilitate both access and surety of supply for patients.

GPhA is a leading constituency and advocate for biogenerics: Our membership includes over 70 generic manufacturers and distributors of finished generic products. Combined, GPhA's members' products are used in nearly two billion prescriptions every year. GPhA's mandate is to support our members efforts to improve the lives of consumers by providing timely access to safe and effective, yet affordable, pharmaceuticals. With healthcare costs rising to unsustainable levels, nowhere will GPhA's mandate be more important than in the area of biological medicines, where the opportunity to impact both collective payor, and individual patients' costs are significant.

Among all pharmaceuticals, biologics are the most costly and thus present the greatest need for increased affordability and offer the potential of significant gains with regard to patient access. In 2009, biologic drugs accounted for 20 percent of the nation's drug spend or approximately \$60 billion. By 2014, over half of the top 100 selling drugs will be biologics. The average daily cost of a biologic product is approximately 22 times greater than a tradition drug. The Congressional Budget Office estimates that biosimilars could save the US healthcare system \$7.1 billion over the next ten years. The biogeneric pathway in the BPCI Act is the key to lowering pharmaceutical costs over the next several decades, yet we are also sensitive to it containing multiple "landmines" that, without FDA's leadership and use of the discretion awarded the Agency by Congress, could hamper the true intent of the law – bringing low cost, high quality biogenerics to the American public. These include, but are not limited to 12 years of exclusivity for branded products, an unwarranted and ambiguous distinction between biogenerics and interchangeability, and the possibility of excluding entire product classes from the pathway. For any meaningful results to accrue from this pathway, FDA will have to be hyper-vigilant in using the most advanced scientific methodologies and technologies to evaluate abbreviated biogeneric applications.

The Biogeneric Pathway – Overall Comments

In theory, the establishment of an abbreviated pathway for biogenerics creates the potential for competition for every biologic. In practice, however, there are barriers that may well prevent use of the pathway, subsequent access and uptake in the market place and therefore any meaningful savings from biogeneric competition, and so no increased access to treatment for decades. Indeed the pathway may not be abbreviated at all, given that the statute has so many specific requirements over and above those required in the PHSA already for 351(a), so-called full BLAs, for originator products (which will always be the biologics that we know the least about at the point of initial approval).

These barriers are of great public health concern and include:

- The expense of developing a biogeneric, and any requirements in 351(k) applications that are unnecessary for the assurance of the quality, safety, purity and potency of the licensed biogeneric product;
- The data exclusivity period of the innovator biologic and/or complexities of the patent exchange process, including requirement for the sharing of the biogeneric 351(k) application and “such other information that describes the process or processes used to manufacture the biological product” with originator, that intimidate or potentially outright block biogeneric sponsors;
- Uncertainty surrounding the information required for a biogeneric application and concurrent or subsequent interchangeability determination

While some of these extend well beyond the jurisdiction of the FDA, they should not be used as reasons not to clarify the regulatory expectations for biogenerics that the Agency has on the issues over which the FDA does have authority, and this needs to happen as soon as possible. The scientific feasibility of developing a biogeneric is not a barrier to competition, since by definition these are products that have already been developed and previously approved by FDA reviewers, and some have already been approved to the highest regulatory standards in other jurisdictions as biogenerics (also recognizing that no other jurisdiction has the option to designate such products as interchangeable with their reference product).

A. Biosimilarity

1. *What scientific and technical factors should the agency consider in determining whether the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components?*
2. *What scientific and technical factors should the agency consider in determining the appropriate analytical, animal, and clinical study or studies to assess the nature and impact of actual or potential structural differences between the proposed biosimilar product and the reference product?*
3. *What range of structural differences between a proposed biosimilar product and the reference product is consistent with the standard “highly similar” and may be acceptable in a 351(k) application if the applicant can demonstrate the absence of any clinically meaningful differences between the proposed biosimilar product and the reference product?*
4. *Under what circumstances should the agency consider finding that animal studies or a clinical study or studies are “unnecessary” for submission of a 351(k) application?*

The cornerstone of the abbreviated biogeneric pathway is the analysis that FDA will undertake to assess comparability. Any and every unnecessary test or study suggested as needed by the FDA has the potential to make an application impossible or infeasible, as well as being ethically questionable. Even if not an outright barrier, it will add to the cost of development for no greater assurance of the quality, safety, purity or potency of the

final products. This will undermine the incentives for sponsors to submit biogeneric applications, and limit the ability of biogeneric products to increase access to more cost-effective therapeutic options for patients and their providers.

Fortunately, biologics and comparative product assessment is an area where FDA has significant experience. FDA has been evaluating originator products for biosimilarity, including the assumption of interchangeability (discussed more below), for years. This is done every time a branded biologic manufacturer changes its manufacturing process, such as making a piping modification, moving processes between buildings or adding new facilities (locally or even internationally), substituting an ingredient or even changing the master cell line. Some of these changes are quite extensive, including the case with Betaseron and Avonex where the FDA use of comparability was challenged and upheld by the courts². FDA worked with the biopharmaceutical industry to develop the original and now well-established protocol for evaluating all these kinds of changes based on a time-honored standard “Comparability”, and led the world into the discussion by the publication of the 1996 Guidance³.

This initiative was followed by a more general adoption of comparability in the highly regulated markets, and ultimately in the generation of the internationally harmonized guidance, ICH Q5E⁴. In the US, this ICH guidance went through full notice and opportunity for comment, and notification of the final guidance in the Federal Register⁵. The originator biopharmaceutical industry participated extensively throughout, PhRMA having the lead role for industry at ICH. As the FDA well understands, having been such a leader on this issue, “comparability” between biological products is defined as “highly similar quality attributes.” Sometimes, clinical studies are needed after a major manufacturing change, but most often comparability does not require any clinical studies at all. The decision is made by the sponsor with the advice of the FDA on a case-by-case basis, and the same can apply for biogenerics. The fundamental needs for a scientifically-sound, and data-driven approach to assessing manufacturing changes were what led to comparability development, and the same scientific principles were then extrapolated to

² Reference to the Avonex case in 1996 and how the Court deferred to FDA on comparability. See <http://www.fda.gov/ohrms/dockets/dailys/04/mar04/031904/80n-0208-ref0001-19-Tab-11-vol126.pdf> (accessed 23Nov10)

³ FDA Guidance “Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products”, Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), published April 1996. Available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm> (Accessed 22November2010)

⁴ ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. EU: Adopted by CPMP, December 1, 2004, CPMP/ICH/5721/03, date for coming into operation: June 2005; MHLW: Adopted 26 April 2005, PFSB/ELD Notification No. 0426001; FDA: Published in the Federal Register, Vol. 70, No. 125, June 30, 2005, pages 37861-37862. <http://www.ich.org/LOB/media/MEDIA1196.pdf> (Last accessed 17November2010)

⁵ Published in the Federal Register, Vol. 70, No. 125, pages 37861-37862, 30 June 2005, notice of the final guidance available at <http://www.fda.gov/ohrms/dockets/98fr/05-12908.htm> (last accessed 17 November 2010)

products from different sponsors in Europe⁶, and became the scientific basis for the equally rational approach to biogenics in Europe. The international comparability standard, ICH Q5E, is now in use all over the world, and was also considered by WHO in the development of their biogenics guideline⁷.

The ultimate goal of the ICH comparability exercise is to establish a reasonable expectation of a continuation of safety, purity and potency after a manufacturing change – and the greater the change the more the potential for differences and so the greater the data burden on the sponsor to ensure that no such a change has occurred. The label of the product does not change and so neither the physician nor the patient knows that the change has occurred – the ultimate in an interchangeability designation. The same review divisions at FDA evaluate comparability for manufacturing changes on originator products – albeit routinely at the CMC level and rarely are clinical reviewers involved. For biogenics, the review divisions that evaluated the reference products will evaluate the 351(k) applications and so will have the pertinent experience both with the original approvals and with the subsequent changes. This is unlike small molecule drugs where an entirely separate office, the Office of Generic Drugs, reviews generic drugs applications. There are no rules associated with the use of comparability as to how the transition between the pre-manufacturing change product and the post- manufacturing change product are managed in the market place, and both can be available concurrently in the marketplace at the same time.

The affirmative demonstration of comparability based on fundamental scientific principles will be no different for a biogeneric and its reference, than for any product originator or biogeneric, pre and post manufacturing changes. Thus, a biogeneric with a different sponsor, and no access to the trade secret development history of the originator reference product, could be said to present the most extreme version of comparability exercise.

A demonstration of comparability entails a series of comparative studies between the two products at issue – pre and post manufacturing change product, or originator versus biogeneric. As a first step the sponsor compares physicochemical and biological attributes, including purity, between the two products. This cannot be achieved with any single test, and a series of overlapping analytical tests are used that measure of a variety

⁶ Guideline on Comparability of Medicinal Products containing Biotechnology-derived Proteins as Active Substances: Quality issues (CPMP December 2003)

<http://www.emea.europa.eu/pdfs/human/bwp/320700en.pdf> (Last accessed 17 November 2010)

⁷ EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION, Geneva, 19 to 23 October 2009. GUIDELINES ON EVALUATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS (SBPs). Available at: http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf (accessed 1 December 2010)

of different parameters – the so called orthogonal approach⁸. FDA also used this concept in recently approving the “biogeneric” enoxaparin⁹, a complex mixture of sugar molecules obtained from natural sources, and while currently regulated under the FD&C Act as a drug, is a biologic in science. The science necessary for this sophisticated comparability exercise is available today and is routinely used for manufacturing changes to the very products that will be the reference products for biogenerics. If no differences are found, then step two is to conduct non-clinical studies using an appropriate *in vitro* or *in vivo* animal model. The aim of the non-clinical studies is to confirm comparability and to detect any potential differences between the biogeneric and reference product that could justify further study in the clinic.

The focus of much of the biogenerics debate has been on the need for clinical testing in human patients, not least because this is the biggest cost barrier to biogeneric competition, yet is often the lowest fidelity comparability screen if the studies are to be conducted on at a feasible scale, and indeed based on the use of comparability with the very same reference products by the FDA to date, may be entirely unnecessary.

As a general principle, clinical testing should not be required to any greater extent that it is required for originator products under-going manufacturing changes, and should reflect the extent of “high similarity” demonstrated at the analytical level. This would match the clinical experience accumulated in the literature, by the medical community and by the FDA, in the very same review divisions, from the use of the reference product over at least 12 years. To require scientifically unnecessary clinical studies would be unethical (as was also raised at the public meeting by a number of speakers¹⁰). Such potential ethical concerns with requiring duplicative product testing, in animals, healthy volunteers and even patients cannot be ignored by the FDA. Biogeneric sponsors, just like originators of products today, will be using highly-sophisticated analytical and validation tools that allow for detailed confirmation of the similarity of biological products¹¹. And the resolution of these tools are rapidly and continuously improving and while this helps

⁸ Reference to the NYAS, NIST FDA meeting in NY, December 2005. where orthogonal approaches were discussed. Detail available at <http://www.nyas.org/Events/Detail.aspx?cid=f60ec694-91e2-471e-a70f-4fe6aec8557d> (accessed 1 December 2010)

⁹ FDA News Release, “FDA Approves First Generic Enoxaparin Sodium Injection”, 23 July 2010. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm220092.htm> (accessed 23 November 2010)

¹⁰ Could list here, but probably unnecessary so could just refer to the general site

¹¹ Docket No. FDA-2003-P-0273 Reference to FDA Enox CP, The five criteria involve (1) the physical and chemical characteristics of enoxaparin, (2) the nature of the source material and the method used to break up the polysaccharide chains into smaller fragments, (3) the nature and arrangement of components that constitute enoxaparin, (4) certain laboratory measurements of anticoagulant activity, and (5) certain aspects of the drug's effect in humans. General information page: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm220018.htm>, and the FDA response to the Sanofi-Aventis Citizen Petition available at: <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM220083.pdf> (accessed 23 November 2010).

all sponsors to thoroughly characterize their products, the significance of any differences found are often less clear¹².

Accordingly, any clinical development required must be need-based and should take into account the degree of similarity demonstrated at Steps 1 and 2. If the biogeneric has been demonstrated to be highly similar analytically to the reference product, it is appropriate to rely on the established safety and efficacy profile of the reference product.

Fundamentally, GPhA sees no justification for anything extra being required of a biogeneric sponsor that is not expected of an originator sponsor when undertaking a major manufacturing change using comparability. To the extent that the statute suggests certain studies, the FDA needs to consider their necessity, and then use the authority also given the Agency by Congress to waive any studies that they consider to be unnecessary.

B. Interchangeability

1. *What factors should the agency consider in determining whether a proposed interchangeable biological product can be “expected to produce the same clinical result as the reference product in any given patient?”*
2. *What factors should the agency consider in evaluating the potential risk related to alternating or switching between use of the proposed interchangeable biological product and the reference product or among interchangeable biological products?*

GPhA finds it impossible to reconcile much of the discussion at the public meeting, and beyond, regarding the very feasibility of interchangeability for biogenics. Some have suggested, on the one hand, that it is impossible to establish biogeneric interchangeability and that the FDA has no standard by which to do this, yet, on the other hand, brand biologics are deemed automatically interchangeable (without even the pharmacist knowing they are substituting biologics) once they are shown to be comparable. These changes made by the originators can be substantial such as a new master cell line, or a major process change such as from roller bottles to fermentation tanks, and these will likely result in product changes including altered glycosylation. The FDA authority to use comparability as the basis for regulatory decision making has been tested in the courts, and FDA’s authority affirmed¹³.

From a scientific perspective, there is no possible justification for treating biogenics differently from originator biologics. And indeed if the scientific concept of comparability (discussed in detail above as the basis for biosimilarity) is used for

¹² Better analytical tools create an issue unto themselves, as the increasing ability to see differences between batches of approved products, between biologics before and after manufacturing changes, or, in the future, between a biogeneric and their reference product either pre or post approval, does not in and of itself indicate that the difference is of any clinical significance.

¹³ Berlex Laboratories vs. FDA. Court decision available at <http://www.fda.gov/ohrms/dockets/dailys/04/mar04/031904/80n-0208-ref0001-19-Tab-11-vol126.pdf> (accessed 23Nov10)

biogenerics, the entire safety and efficacy history of the reference product is as relevant to the biogeneric as it is to the originator biologic itself when making a manufacturing change. As such is erroneous to even suggest that the data set for the biogeneric even when initially approved is smaller, and imply, on that basis, that the safety of the biogeneric is in any way less than the post-manufacturing change originator. Indeed, if FDA uses the comparability standard consistently in all cases, it would mean that the data set for a biogeneric at its point of approval is necessarily greater than for the reference product at that same point in time¹⁴. Further a biogeneric will be as much the same as its reference, as a reference is to itself pre- and post a manufacturing change. And in the latter instance patients and their physicians are not even told a change has been made. The same standard for all biologics applied fairly by the FDA to all sponsors, will assure patients and their physicians that both originator biologics and biogenerics are as safe and effective when they reach the market – this confidence is crucial to good patient care. GPhA also agrees each application from each sponsor is stand alone, and is respected as trade secret, but GPhA believes that FDA can use the standard already developed and represented by information in the public domain including the reference product label, alongside the comparability/highly similar standard, used by FDA for manufacturing changes (and in other highly regulated markets also for biogeneric approvals), and apply it consistently to all sponsors. Further, the equivalence determinations used for biologic drugs approved as 505(b)(2)s or as generic biologics, and the reasoning behind them can contribute too¹⁵.

The requirement of mandatory switchability studies for biogenerics also raises questions. Such studies are not required when innovators make minor or major changes to their products. Therefore, if the comparability standard is met analytically switchability studies should not be necessary.

To be clear, GPhA believes that FDAs experience with the assessment of the reference biologics both when they were originally approved, and subsequently during capacity expansion or other manufacturing changes is direct evidence of the Agency's ability to evaluate biogenerics. The FDA has an interchangeability standard and in the context of manufacturing changes it is called comparable¹⁶. In the context of previously approved biologics in science that were approved as drugs, the standard has been called highly similar¹⁷ or equivalent¹⁸. In all cases the science is the same. The standard applied is as

¹⁴ With no public information on the biogeneric, prior to approval, its data is not in the public domain, whereas the entirety of the originators data set, public or private, is pertinent to the biogeneric simply through reference to the current originator label

¹⁵ FDA has approved 2 ANDAs, and 8 505(b)(2)s a biologic drugs, and all raised issues that are pertinent for biogenerics, and that the FDA has previously resolved. That experience is of value for the evaluation of biogenerics, as a scientific and regulatory matter.

¹⁶ ICH Q5E – see above

¹⁷ See Omnitrope CP response in which comparability is used 28 times. FDA response to the Citizen petitions of Pfizer, BIO and Genentech, and specifically addressing Omnitrope. Available at <http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf> (accessed 1 December 2010)

similar as that science allows¹⁹, and the variable is the data burden, which is always case-by-case and unique to any given sponsor irrespective of their business model.

GPhA agrees that when two products are comparable/highly similar, it is usually appropriate that there is:

- No change in the products label, including no change in the USAN²⁰ (INN²¹);
- No required preclinical studies, although they are occasionally required;
- No required clinical studies, although they are rarely required;
- No withdrawal of product so two and sometimes three different versions of the product can be in circulation at the same time, and patients can be switched between them without any studies have been done to assess any risks with such switches;
- No additional/repeated pharmacovigilance studies;
- No advisories sent as “Dear Doctor” or “Dear Pharmacist” letters to those most directly dealing with the patient, indeed neither the Doctors, nor the Pharmacists know that a change has occurred, although the latter can observe a change in batch number.

However the same confidence in the science of comparability should also be applied to biogeneric sponsors. The data burden on sponsors should also be irrespective of the traditional business model of the applicant, and an assumption of a greater degree of clinical assessment for biogenerics than is expected of originator sponsors making manufacturing changes is unfair and scientifically inappropriate. Indeed, as Dr. Woodcock testified at the 2007 Waxman Hearing²², FDA requires clinical studies for less

¹⁸ See enoxaparin CP response where some form of the word equivalent is used 157 times; Further FDA describe the criteria they used: “ the five criteria involve (1) the physical and chemical characteristics of enoxaparin, (2) the nature of the source material and the method used to break up the polysaccharide chains into smaller fragments, (3) the nature and arrangement of components that constitute enoxaparin, (4) certain laboratory measurements of anticoagulant activity, and (5) certain aspects of the drug's effect in humans. See FDA Response to Citizen Petition of Aventis of 19 February 2003. Available at: <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM220083.pdf> (accessed 1 December 2010).

¹⁹ Science never shows identity or “sameness”, just the absence of difference according to the specifics of the criteria used. Hence, there is a risk to the better analytical techniques, as they will, indeed should, find more difference between test batches of biologics, be they innovator or biogeneric or each with each other. The challenge is the interpretation of those differences in a manner which is useful for the better treatment of patients.

²⁰ United States Adopted names (USAN) Home page. Available at: <http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council.shtml> (accessed 1 December 2010); USAN Naming Biologics. Available at: <http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/naming-biologics.shtml> (accessed 2 December 2010)

²¹ INN Reference – name of the active ingredient and specific designed to assist health care providers, in place since 1953 worldwide and administered by WHO

²² Follow-on Protein Products. Statement of Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer

than 1 in 50 or even 1 in 100 manufacturing changes using comparability, and so this also supports the concept that where sufficient analytical quality data has been provided it will be appropriate for FDA to waive preclinical and clinical studies. Further, given that an originator biologic is ALWAYS interchangeable with itself pre-and post- manufacturing change, this same standard must also be achievable for biogenerics based on the same flexible data expectation. For some products there will be greater or less confidence, and GPhA is not adverse to FDA caution, but that same caution on what is assumed to be “the same” and what is assumed to be “different” must apply to all uses of the scientific concepts of comparability/highly similar/equivalent. Just as has been the case with originator biologics, the experience with the reference molecule and the reactions by patients over time will contribute to the expectations for biogenerics. However biogenerics through access to this experience (which is quite distinct from specific originator product development data or the dossier itself, and for instance, includes an extensive scientific and professional literature, accumulated over at least 12 years of use of the reference product), as well as the latest technology will be able to target their development studies²³. As such biogeneric sponsors will be able to much more precisely use analytics to design optimal biogenerics, and the lower fidelity but confidence building preclinical and clinical studies will be useful but largely confirmatory. Preclinical and clinical studies were truly experimental for the originator, but this will not be their value for biogenerics, and given that it is unethical to do unnecessary studies, and in some case impossible, GPhA expects that over time FDA will become more confident in a greater dependence on increasingly higher resolution analytics that demonstrate high similarity, just as is now the case for manufacturing changes to currently approved biologics.

And at a practical level, given the current nature of the US health care system, FDA needs to understand that interchangeability is the engine that most immediately drives competition and support access through affordability. It is the reason why generic drugs have generated savings of \$824 billion over the past decade. While the generic small molecule drug market took a while to evolve, post enactment of Hatch Waxman in 1984²⁴, to the level of efficiency we now see, given that the scientific basis for interchangeability of biologics is already established through the FDA leadership and experience with comparability, there is no reason for biogenerics not to be more rapidly adopted. We do not need to reinvent the wheel for all biogenerics based on rhetorical

Food and Drug Administration before the House Committee on Oversight and Government Reform, March 26, 2007. Available at: <http://www.fda.gov/NewsEvents/Testimony/ucm154070.htm> (accessed 1 December 2010)

²³ Biogenerics represent ideal systems in which to test other regulatory initiatives of the FDA such as Quality by Design. See Q&A available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM210822.pdf> (accessed 23 November 2010)

²⁴ Drug Price Competition and Patent Term Restoration Act of 1984, also known as Hatch Waxman.

Summary available at [http://thomas.loc.gov/cgi-](http://thomas.loc.gov/cgi-bin/bdquery/z?d098:SN01538:@@@D&summ2=2&TOM:/bss/d098query.html)

[bin/bdquery/z?d098:SN01538:@@@D&summ2=2&TOM:/bss/d098query.html](http://thomas.loc.gov/cgi-bin/bdquery/z?d098:SN01538:@@@D&summ2=2&TOM:/bss/d098query.html) (accessed 6 Dec 10)

arguments around terminology as if it has ever been accepted that generic drugs are identical with their reference products. The very credibility of the FDA data-based decision to approve interchangeable biogenerics is crucial. Given that no-one else is either qualified nor will see the actual scientific data on any product, the FDA must not allow their role in directly reviewing data, as delegated to them by Congress in the new pathway, to be usurped by other potentially less neutral and certainly less science-driven interests. The way that FDA deals with interchangeability will be directly responsible for the market dynamics resulting from use of the biogeneric pathway and thus for the consequences in public health terms through utilization of biogenerics. Without an FDA willingness, when justified with data, to designate biogeneric biologics as interchangeable to the same extent as they do today pre- and post-manufacturing changes, we can expect to see detailing wars that are a net cost for all sponsors and that must be passed on to the payors and their patients. The expectation of Congress, in enacting legislation, was for biogeneric sponsors, including both GPhA members and traditional originator companies, to put price pressure on originators whose patents and exclusivity have expired, thereby forcing prices down for consumers and the government, and ensuring savings in the billions over the next decades. This will also free up resources for investment in the next generation of medicines, as well as enable wider access to the older ones, and so enable better health more broadly. Such competition is the mainstay of the American free-market system, and the only difference for biologic sponsors is that FDA licensure is a necessary step prior to reaching that market.

Thus, FDA should be exceedingly reluctant to elevating the interchangeability to a level that is unnecessary for quality, safety, purity or potency reason or unattainable. The standard imposed on originator sponsors for their own products has to be the standard in which FDA feels an appropriate confidence or the Agency should not have been using it for the past 14 years, and as such it is also the fair and correct standard for biogenerics. It should be noted that the statutory language does not use of the term “higher standard” for interchangeable biosimilars (a term used in the Federal Register notice²⁵), possibly because no-one should be suggesting that not-designated-as-interchangeable biogenerics will be being approved to a “lower standard”²⁶. While, without any FDA waivers, data burden of an interchangeable biogeneric will likely be greater, the product itself will be the same, and indeed some sponsors could decide to submit for an interchangeable biogeneric as a single 351(k) application rather than engage in two review cycles, whereas others may elect to seek a biogeneric approval first and submit for interchangeability as a supplement.

²⁵ Quote from the Federal register notice “To meet the higher standard of “interchangeability,” a product shown to be biosimilar must also demonstrate that it can be expected to produce the same clinical result as the reference product in any given patient and, if the biosimilar product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biosimilar product and the reference product is not greater than the risk of using the reference product without such alternation or switch. Interchangeable products may be substituted for the reference product by a pharmacist without the intervention of the prescribing health care provider.”

²⁶ If indeed FDA considers that there is a difference in standard, GPhA and like many others seeks clarification as to what this is envisaged to be.

C. Patient Safety and Pharmacovigilance

1. *What factors unique to proposed biosimilar or interchangeable biological products and their use should the agency consider in developing its pharmacovigilance program for such products?*
2. *What approaches can be undertaken by the agency, industry, or health care community to ensure appropriate pharmacovigilance for biosimilar and interchangeable products?*
3. *Assuming each product is given a unique nonproprietary name, should a distinguishing prefix or suffix be added to the nonproprietary name for a related biological product that has not been demonstrated to be biosimilar, a biosimilar product, or an interchangeable product to facilitate pharmacovigilance? What factors should be considered to reduce any negative impact on the healthcare delivery system related to unique nonproprietary names for highly similar biological products?*
4. *What safeguards should the agency consider to assist the healthcare community when prescribing, administering, and dispensing biological products to prevent inadvertent substitution of products not identified as interchangeable without the intervention of the prescribing health care provider?*
5. *What are some mechanisms that FDA may consider to communicate findings that a particular product is or is not biosimilar to or interchangeable with a given reference product?*

First and foremost a biogeneric will be a biologic, just one on which comparative studies have been conducted as well as standalone studies, and one on which there is a previously approved product about which a considerable amount is known, both about the product itself and about its use in the practice of medicine over at least 12 years. This will enable much greater history and context to a biogeneric licensure than is ever the case for the newly-approved truly innovative originator product. Nonetheless, just like any other biologic, FDA will review the dossier, consider and assess the scientific justification for every step in its development, and license the biogeneric based on the entirety of the data package submitted by the sponsor. The prior knowledge will add confidence, but the key data on which the FDA decision will be made will be that assembled by the biogeneric sponsor on their product relative to the data that they assembled on their chosen reference biologic in head to head studies. And given the expectation that FDA must apply consistent standards to all biologics, irrespective of the business model of the sponsor, and that this review will be within the same review divisions at the FDA²⁷, it is a fair expectation that any biogeneric that is licensed will be as safe and as effective as any

²⁷ All reviewers need to be working to the same standards and review practices throughout the review of all biologics – this cannot mean that, for instance, biogeneric applications are assessed by clinical reviewers but comparability applications to support manufacturing changes do not. Good review Practices must apply equally, see <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm118777.htm> (Accessed 23November2010)

other biologic approved by the FDA. Thus, the initial FDA approval decision becomes the basis for the same post-marketing expectations, albeit only to the extent that the questions have not been asked and answered by the studies done during the period of exclusivity of the reference product when only that product was on the market (a minimum of 12 years). Again, the standard must be based on consistency, and the collection of all clinical data must have appropriate scientific justification – and this includes feasibility and ethics. GPhA believes that consistency in the application of regulatory standards by the FDA applies throughout the lifetime of the product, and hence to post marketing as well as pre-marketing studies. This consistency should mean that the post-marketing obligation on biogenerics does not exceed that on originator biopharmaceuticals, and further that the knowledge learnt from the reference product should be appropriately integrated into the studies expected of biogeneric sponsors.

This same question arose in Europe after the first few biogeneric were approved in Europe, and the anti-biogeneric detailing became a source of some frustration for EU regulators, given that it strongly implied that at the point of initial approval the products were less good. Nicolas Rossignol, then Administrator of the EC's pharmaceuticals on questions of safety for EU biosimilars was quoted:

"I don't judge case by case, but I have a message: we have promoted and developed with the European Medicines Agency a special biosimilars framework. So we are confident that if a product meets all the requirements and gets a marketing authorization from the commission, it means that the product is as safe and effective as any other product authorized by the commission"²⁸.

Many of the issues that have been brought up in the context of the biogenerics debate actually apply to all biopharmaceuticals and this includes appropriate record keeping to enable tracking and tracing adverse events to individual products, or individual batches of individual products as was needed for the oft cited post-manufacturing-change induced problems with PRCA that occurred in Europe. These were not issues of safety for biogenerics, and were not used by the sponsors of the originator products to which they applied as evidence against the future use of comparability, as might have seemed more appropriate to the specifics of the circumstances. GPhA supports the appropriate use of comparability, and also the availability of biogenerics and for both appropriate and consistent science-based decision making is needed from the FDA. To the extent that data is necessary on individual products once they are on the market and being used by patients it must be collected consistently for all biologics – including currently approved 351(a) products about which some participants at the FDA public meeting have doubts concerning the traceability. It is worthy of note that any issues to date in the US with biologics must be with the originator biologics as only these are available, and perhaps it is more appropriate to discuss these issues in a forum where the implication is not that it is the biogenerics that will be creating a unique new concern.

²⁸ SCRIP World Pharmaceutical News 24 April 2008, reporting on EGA Meeting, London

The FDA has also raised the naming issue in the Federal Register notice, although it should be noted that the naming question is not raised or the existing system changed in any manner in the BPCI Act, and as such Congress has not given any direction to the FDA to in any way alter the current system. We would also note to date there has been no debate over the use of the same generic name (international non-proprietary name - INN, or US Adopted Name – USAN) for biologics approved as full NDAs (505(b)(1)s) or BLAs (351(a)s), and many have shared the same generic name, and no safety issues have arisen due to confusion, or been cited by those proposing the need for a unique INN/USAN for biogenics^{29,30}. Likewise in Europe the majority of the biogenics have appropriately been given the same INN as their reference product, and GPhA supports this as these products have been shown using the very rigorous comparability approach to have the same active ingredient³¹. Nonetheless the biogeneric is fully distinguishable from its reference product through a different brand name and manufacturer, and this in combination with the INN (which allows pooling of data, and reduces the risk of double dosing³²) and the batch number makes for the necessary data set for sound track and trace during physician prescribing, pharmacist dispensing and patient use. We would observe that any post-market surveillance system, however perfectly designed, can never compensate for the failure to collect the necessary data. Thus, GPhA supports continuation of the current system, but with better data collection for all biologic usage rather than a redesign of the system for no improvement through the failure to collect the necessary data, and probably a great increase in confusions. Those responsible for recalls of medicinal products when there is a safety concern were able to indicate their ability to do so rapidly with the current system and using the NDC number. We defer to their experience, and also to their like conclusion that the INN of a biogeneric should be the same as that of its reference product. However, GPhA maintains that the use of different names for biogenics undermines the underlying need for improved data collection, such as lot numbers, for all pharmaceutical products.

The goal of pharmacovigilance and risk management plans for biogenics more broadly, just as for originator biologics, are to support the safe use of biopharmaceuticals and thereby to ensure patient safety. The familiarity gained with the reference product, and scientific progress may mean some studies do not need to be repeated or will be different,

²⁹ Many products that have never been compared share the same INN, for example the somatropins, others that have been compared and failed comparability share the same INN, for example Myozyme and Lumizyme (both have the same INN ALGLUCOSIDASE ALFA). While a demonstration of comparability has never been a criterion for sharing an INN, the fact that biogenics will have highly similar active ingredients is a basis for having the same INN since the INN is the name of the active ingredient and not of the product, and was always intended to advise physicians, and is not the basis for prescribing. Historically the FDA is on the record with supporting the continuation of the current system –find 2006 letter to WHO, and it is not apparent why the FDA would revisit this issue now.

³⁰ BioCentury “Myozyme’s zig zags”, Volume 16, Number 48, Pages A1-6, 27 October 2008

³¹ See the EU Public Assessment Reports (EPARs) for each biosimilar available on the EMA home page for EPARs available at: (accessed 6 December 10)

³² An interesting suggestion made by Dr. Kozlowski during the Q&A at the public meeting and not adequately answered by the presenters to whom it was asked

but again the goals are identical for all biologics, whether originator, biogeneric or alternative biologics. Indeed appropriate use and monitoring is needed for all medicines, and there is no valid scientific or clinical basis on which to assume risks to patients are greater for biogenerics, and indeed will much likely be less than for innovator products, due to the prior experience with the reference product as well as biomanufacturing improvements subsequent to the originator approval. All medicines, both biologic and drug, originator and generic, need to be used carefully, and complete records kept. For generic drugs, the product labeling is identical, and bound by that of the originator, but for biogenerics it is expected that the labeling of the biogeneric will vary from that of the originator. GPhA would not like to see a problem with an originator biologic attributed to a biogeneric, any more than we would like to see a problem with a biogeneric attributed to an originator product – neither benefit any sponsor nor facilitate the rapid resolution of any concerns with any particular product. Such comments made at the public meeting were neither helpful nor appropriate, and ultimately were misleading.

The availability of biogenerics will not change the need for good track and trace, and so existing mechanisms should be evaluated and any necessary changes applied to all medicines in the future. As a practice of medicine/pharmacy issue this is beyond the responsibility of the FDA, but clear labeling will always help the appropriate use of any product. GPhA does not support the labeling of biogenerics as not being interchangeability with their reference product³³. We do not do this today for related products, not even for products that have the same active ingredients and share INNs, and there is no evidence of any risk to patients that has resulted. And if a product is not biogeneric then it will not be approved through the new 351(k) pathway, and if approved as a BLA can be treated in the same manner as any another new product is today – it will have its own labeling that assures appropriate use to the best extent possible. If approved as biogeneric the label will reflect this, and likewise for an interchangeable biogeneric. No biogeneric will be a reference product for another biogeneric. Ultimately, the regulatory decisions made by the FDA for any product are independent of those for any other product. While there may be shared concerns and data analysis on classes of product that lead to advisors, ultimately each sponsor communicates with the FDA in the context of their particular product and we see that continuing in a world that has biogenerics, along with originator drugs and biologics and generic drugs.

D. The Use of Supportive Data and Information

³³ FDA has a long practice of managing pharmaceutical equivalent products not designated as interchangeable, without any indication on the label itself. For example, Levothyroxine. FDA Questions and Answers on Levothyroxine Sodium Products. Available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm161266.htm> (accessed 6 December 2010)

1. *From a scientific perspective, to what extent, if any, should animal or clinical data comparing a proposed biosimilar product with a non-U.S.-licensed comparator product be used to support a demonstration of biosimilarity to a U.S.-licensed reference product? What type of bridging data or information would be needed to scientifically justify the relevance of the comparative data?*

The legislation authorizing FDA to implement the biogeneric/interchangeable pathway in the US in March 2010 occurred many years after the legal revisions that allowed biogeneric products to be approved in Europe³⁴. Also the patent expiry issues on key reference products in Europe are substantially different from those in the US. Europe had established their new biogeneric pathway as part of an overall reform of their medicine laws, and does not have the challenges of two statutes that the FDA has to consider, but nonetheless has had to deal with many of the standards issues that FDA now faces. At the FDA public meeting, many presenters representing a wide variety of stakeholders, endorsed the transparent process that Europe took in enabling the first generation of biogenerics to be approved in a highly regulated market³⁵, and GPhA supports FDA using all available means to build on the successful experiences in Europe that have made quality, safe and effective biogenerics available there in a manner that minimizes unnecessary repetitions of activities by the Agency or by sponsors.

Europe has developed and finalized multiple guidelines, and this was done concurrently with the development of the first generation of biogenerics, and they were published only shortly before the first approvals. As EMA has learnt more, through the submissions and discussions surrounding science advice with sponsors, so they have come to realize that some of the guidelines for biogenerics need to be revised and they have started this process for Epoetin³⁶. Nonetheless, the process was transparent, the guidelines are public, were subject to public discussions, and they have been adopted in their entirety by some countries, such as Australia. Fourteen biosimilars have now been approved in Europe, and for each a guideline was available prior to approval, albeit not prior to the initiation of development. The development of each took years, so one significant downside is the timeliness of any FDA guidance development. It becomes all the more important that FDA extrapolates from the EU experience, and does not simply repeat it.

Given that the EU requires a European reference product and that Europe is substantially ahead of the US, it means that the FDA, more than EMA, is faced with the question of

³⁴ Directive 2004/27/EC. Available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2004_27/dir_2004_27_en.pdf (Accessed 11November2008), and Regulation (EC) No 726/2004, available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf (Accessed 11November2008)

³⁵ GPhA is using the term biogenerics for those products approved based on a demonstration of “high similarity” or “interchangeable” with their reference products, products for which this is not the case we are calling alternative biologics.

³⁶ Concept Paper on the Revision of the Guidance on Similar Biological Medicinal Products Containing Recombinant Erythropoietins available at: <http://www.emea.europa.eu/pdfs/human/biosimilar/17073408en.pdf> (Accessed 23November2010)

how much data, and how pivotal/supportive can that data be, for a US biogeneric application if it is comparing a biogeneric to an EU reference product and not to a US one, even if the only difference is the label on the vial. This is a situation that various jurisdictions have addressed differently, with Canada potentially allowing a non Canadian reference product, Australia on its face requiring an EU one (albeit one expects that a Australian one would also be acceptable), and the US in the statute requiring a US 351(a) reference product. However, in the US this could be by a modest bridge of data such that every single comparative study for a US biogeneric application does not have to be with US-labeled product, or it could be that the FDA chooses to require a repeat of every single study with the US reference, and beyond that in terms of additional studies. The discretion between the multiple potential extremes is left up to FDA, and GPhA would hope that FDA will choose the science-based rational middle, that treats all products consistently. Nothing in the statute requires every study in support of a US biogeneric be conducted in parallel with the US labeled product. These types of review decisions fall within FDA's discretion, and should follow the science and the specifics of the application.

Further, today, we have originator biologics that are based on one set of data, including the necessary preclinical and clinical studies, but that are able to be approved in multiple jurisdictions and patients in many cases are supplied globally from single facilities. Through ICH and various other international organizations such as the World Health Organization (WHO) (recognizing that WHO is not a formal regulatory authority), as well as through the efforts of individual regulators, there have been extensive efforts to harmonize the regulatory requirements for originator biologics to minimize the burden on sponsors to repeat expensive studies unnecessarily. Indeed, through the Common Technical Document (ICH CTD³⁷) we are increasingly supporting a single dossier applicable in multiple jurisdictions too. Any savings in development can reduce the cost to patients, without any compromise is the quality, safety and efficacy of the final product (indeed better confidence as the data sets pre and post approval from multiple jurisdictions can be more readily pooled). This harmonization is far from complete, and has tended to be subsequent to regional regulations which must then be reconciled, but data is increasingly broadly applicable, irrespective of where the studies are conducted, and the dossiers increasingly so. This is quite appropriate.

Regulatory harmonization is a goal that GPhA supports for originator biologics both because such repeats would be unethical in their use of animals and clinical trial subjects, and because the use of resources would preclude some patients in some jurisdictions (especially smaller and poorer countries) access to these critical medicines. However, that same logic must also apply to biogenics – both as a fairness issue, but most fundamentally because repeating all studies for each authority with their particular reference product is even more clearly scientifically unnecessarily and unethical for

³⁷ ICH Common Technical Document, available at <http://www.ich.org/cache/compo/276-254-1.html> (accessed 23 November 2010)

biogenerics, and it will not be economically feasible for products to be cheaper for payor/patients if excessive and or unnecessary studies are required.

Given that systems are already in place whereby studies done outside the US can be acceptable, these can be readily applied to supply data for biogenerics too. However the additional steps needs to be made, as these regulations and practices do not cover the use of local or other ex-US reference products when it comes to US license applications. GPhA strongly supports the appropriate bridging, on a scientific basis, with the burden always remaining on the sponsor to justify relevance and sufficiency, of data collected with ex-US reference products such that unnecessary or unethical studies are not required by the FDA, and this includes duplicative studies, but also the entirety of the development plan. A scientifically-based bridge to the US 351(a) approved product is needed but not a repeat of the entire dossier. As stated above, nowhere does the new BPCIA statute require every study in support of a US biogenic 351(k) application to be conduct in parallel with the US labeled product. In sum, GPhA acknowledges that FDA needs, as a legal matter, to have made a prior decision to approve a 351(a) reference product before they approve a biogenic to that specific product, but supports consideration being given to a closely related biogenic already approved and marketed in another highly regulated jurisdiction, and how it might be expeditiously bridged to a US 351(a) reference product. The biogenic sponsor has to support the relationship of the ex-US reference product and the FDA licensed 351(a) reference biologic with data. Given that FDA is limited to the statutory language referring to a previous 351(a) approved product, the overall objective can be achieved by the FDA using its waiver authority carefully but appropriately to acknowledge scientific data that bridges the foreign reference product to a US reference product based on the highly similar standard.

Clearly, one of the most immediate ways for FDA to be proactive is to support biogenic applicants using data previously generated outside the US in other highly regulated markets, and encourage them to appropriately build on these studies and provide justification or add additional data that appropriately connects the EU efforts to the chosen US 351(a) reference product. The entirety of this data set then forms the US biogenic application. Just as the sponsors of originator biologics use data from multiple locations, the same must be allowable for biogenic sponsors if they are to be able to develop and manufacture biogenerics to fulfill a global need and maximize efficiency in development for the US market. And indeed this allows for a more complete data set on which the FDA can make the appropriate review decisions. Scientifically sound flexible approaches will maximize the availability of quality, safe, pure and potent biologics of all types, with the minimal unnecessary repetition on studies. It is an issue of regulatory consistency and basic fairness that the same regulatory standards are applied to all sponsors of all biologics irrespective of the business model. If each regulatory authority wants unique head to head data with only their domestically approved product, and this includes extensive preclinical and clinical studies, the availability of biogenerics to the patients most in need of them will be drastically curtailed, and the savings even in those markets where they do become available will be vastly less. And the products, if and

when they do become available, will be no better quality or safety, purity and potency as a result, they will simply cost more.

GPhA supports FDA ensuring harmonization through regulatory cooperation with other regulatory authorities (especially those well qualified and experienced in approving biogenics), and expects the FDA to be better able to do this in anticipation of the US implementation of the biogenics pathway than after processes and procedures have become established as has historically been the case for other aspects of the regulation of medicinal products in the highly regulated markets. For instance, if the stakeholders, including the FDA, have no issues with the quality, safety and efficacy of the EU approved biosimilars, then the most immediate priority would be to enable these proven products an expedited way to reach the US market using all the data now available on them. If this is impossible, then GPhA is all the more concerned about the ability of US consumers to get access to these and other biogenics in a timely manner through FDA leadership and use of its new authority. Just as originator products have become global in development and manufacture, so we would hope that FDA would encourage a parallel approach being facilitated by the regulatory expectations for biogenics. Global development enables efficiencies that lower development costs and this can translate into better public health opportunities through increase access. Additional guidance, if needed, must also be flexible to accommodate what can be anticipated to be continuing developments in the underlying manufacturing and analytical technologies associated with all biologics.

More generally, GPhA encourages FDA to take a leadership role in developing a framework for use of foreign reference product data, and data on biosimilars approved ex-US, that recognizes valid science while at the same time preserving FDA discretion on the ultimate questions of quality, safety, purity and potency. This may be one area for FDA to consider specific guidance, given that permitting the use of testing involving foreign reference products will maximize the total data set available to FDA, and enable high-quality safe and effective biogenics to be approved by the Agency more rapidly while minimizing unnecessary and ethically questionable repetitive studies. This is especially the case where the foreign reference product is the same as the U.S. foreign reference product in all ways except the label. Nonetheless, just as for all applications, FDA should seek all necessary and sufficient data, and thereby limit it to what is actionable as a regulatory matter. FDA has the confidence of Congress as delegated in BPCIA to examine this for biogenics, but the need for parity may enable the Agency to revisit some of the legacy expectations that have become requirements for all biologics. For instance, new techniques may be able to replace old, and not simply supplement them.

E. Definition of a Biological Product

1. *What scientific and technical factors should FDA consider in developing a regulatory definition for the category of "protein" (as distinguished from peptide or polypeptide)?*

2. *What scientific and technical factors should FDA consider in developing a regulatory definition for the category of “any chemically synthesized polypeptide”?*

GPhA supports all biologics being approved to the same standards and according to the same criteria. Hence, the greatest priority for FDA is to review all applications, whether NDA or BLA, and whether originator or generic/bigeneric, to consistent regulatory standards, recognizing that the data will always be case-by-case for any product, and will always be unique to that product and that sponsor in the same manner as for originator products. As such the distinction between the FD&C Act approval standards of safety and efficacy should not be distinguishable from the PHS Act standards of safety, purity and potency when it comes down to the expectations of patients and their providers in the practice of medicine. Thus, even when biogenerics can reference biologic drugs (those products that are biologic in science but that have been approved as drugs under the FD&C Act) 10 years after enactment, there should not be any confusion as to the regulatory standard. While the historical situation of some biologics having been approved as under FD&CA and some under PHSA is unfortunate and confusing, what matters is that FDA not let this delay the future availability of generic biologics and biogenerics, and that patient and provider confidence in the FDA “gold standard” of review is not undermined.

The synthetic peptide products that are FD&C Act drugs, and that will not join the other FD&C Act biologic drugs in becoming available as reference products for 351(k) applications on March 23, 2020, must remain subject to Hatch Waxman options as reference products for 505(b)(2) and ANDA applications. While GPhA does not see this as being an open question, FDA confirmation would be particularly helpful for potential sponsors of generic products to these exceptions.

The distinction between “protein”, as opposed to “any chemically synthesized polypeptide” is not problematic for currently approved products that will become available as 351(k) reference products in 2020. Of the FD&C Act currently approved we are only aware of calcitonin and glatiramer acetate as falling into the category of peptide-based, chemically-synthesized drugs (the former is only 31 amino acid in length and so clearly small, and the latter is a complex mixture of small peptides made of four amino acids, and already subject to a number of ANDAs) and so never becoming available as reference products for 351(k) applications. Insofar as calcitonin has been approved as multiple independent products manufactured using a variety of sources, including as naturally-sourced, recombinant and synthetic versions that are all approved as NDAs, there will be the issue that some of these originator products becoming available as reference products for 351(k) applications and the synthetic ones remaining for 505(b)(2) or 505(j) applications. However, this is an unusual instance that is probably best handled by the FDA separately, and not as the basis for biogeneric policy considerations more generally. Nonetheless, GPhA agrees that clarification of the statutory definition of biological product is important and that the FDA’s interpretation of the statute will be useful to all sponsors, not least for originators of future products. Given that, for instance,

the regulatory pathway determines the nature and length of the exclusivity awarded by default at the time of initial approval, the impact on the availability of generic biologic drugs and biogenerics as a public health issue should not be underestimated.

It is GPhA's understanding that the regulatory status of the original FD&CA biologic drug remains unaltered even after 2020, but that future applications for alternative biologic drugs would be as PHS Act 351(a) BLAs. The only future biologics that would be 505(b)(1) applications are the synthetic peptides, and that is where the size distinction in the question above matters, although the term “synthetic” could still be interpreted as governing. Indeed, if FDA were to take “synthetic” as governing, then all proteins are simply accepted as a form of polypeptide (which is scientifically already accepted), and the distinction is in the means of manufacturing – synthetic or not. This then allows the definition to be expressed as the corollary – namely synthetic means made absent a living system, and/or not involving the use of DNA, transcription or translation (since recombinant technology can also be used to make peptides *ex vivo*, although this is currently unlikely to be at manufacturing scale). This would allow future synthetic peptides to be approved under FD&C Act at FDA discretion, and done not require a bright line distinction as to how many amino acids make a peptide, nor how many make a protein.

F. Guidances

1. *What types of guidance documents for industry should be a priority for the agency during the early period of implementation?*
2. *Section 351(k)(8)(E) of the PHS Act permits the agency to indicate in a guidance document that the science and experience, as of the date of the guidance document, with respect to a product or product class (not including any recombinant protein) does not allow approval of a 351(k) application for such a product or product class. What scientific and technical factors should the agency consider in determining if the existing science and experience are sufficient to allow approval for a product or product class under section 351(k) of the PHS Act?*

FDA guidances, both general and specific, can have value to sponsors, but should not be used as a way to delay biogeneric applications. Historically, most FDA guidance has been developed when FDA recognizes that there is an issue, or even opportunity or problem, common to multiple products or a given type of situation, and FDA uses the Agency's acquired expertise and common experience with multiple products to seek further input and then advise all current and future sponsors on best ways to proceed. Guidance is not generally used in anticipation of issues, nor for individual originator products because they often raise unique issues that cannot be foreseen. And guidance does not release confidential or trade secret information about individual products. Drafting and finalizing guidance is resource intensive for both FDA and industry and so should only be pursued if it can be balanced with an expectation of saving effort and resources for sponsors and the Agency reviewers with subsequent applications, or if there

is a particular safety issue that all need to be aware of. And while guidance is not binding on either the FDA or sponsors, it does carry a great deal of influence of how products are developed and reviewed in the future, and so the tendency to constrain future developmental approaches must also be considered.

It is nonetheless fundamental to the development of medicinal products that FDA's forte' is in review, and industries' is in development and manufacturing, and guidance will never be a recipe just as it can never anticipate the truly innovative approaches that we continue to hope to see in products, but also in biomanufacturing methods including characterization as well as production *per se*. Thus, GPhA supports guidance if appropriately prioritized and will look forward to contributing to its development, but an assumption that all guidance is equally valuable to all sponsors is not valid. It is also important that no application, originator or biogeneric, be held hostage to the finalization of any guidances, either general or specific. This includes no delays for specific application-associated guidance such as the routine and regularly scheduled individual sponsor meetings associated with biologics, and certainly GPhA does not concur with the suggestions of some that biogeneric applications in any way defer to originator applications in terms of reviewer priority. The BPCIA does not require the FDA to promulgate any guidance and if traditional timelines are followed, GPhA would expect to see biologics being approved and available to patients long before any biologics guidance is final.

Europe has developed and finalized a series of guidelines for biosimilars, and this was done concurrently with the development of the first generation of biosimilars, and they were published only shortly before the first approvals. As EMA has learnt more through the submissions and discussions surrounding science advice with sponsors, so they have come to realize that some of the guidelines for biosimilars need to be revised, and they have started this process for Epoetin³⁸. Nonetheless, these guidelines are public, were subject to public discussions, and they have been adopted in their entirety by some countries, such as Australia. Fourteen biosimilars have now been approved in Europe, and for each a guideline was available prior to approval, albeit not prior to the initiation of development.

There is no value to FDA re-generating topic by topic the Guidelines in EU, but the Agency should build on the EU progress, and evaluate the US opportunities for biologics most particularly in terms of what is different in their authority from that held by EMA. Also the FDA generally does, and indeed should engage in regulatory cooperation with EMA going forwards to ensure all possible coordination of future EU/US regulatory efforts, including but not limited to guidelines and guidances for biosimilars. We would particularly encourage the FDA to find all means possible to contribute the Agency's experience and expertise to those guidelines already underway in

³⁸ Concept Paper on the Revision of the Guidance on Similar Biological Medicinal Products Containing Recombinant Erythropoietins available at:

<http://www.emea.europa.eu/pdfs/human/biosimilar/17073408en.pdf> (Accessed 23 November 2010)

Europe, such as those just finalized³⁹ and about to be implemented for monoclonal antibodies. To the extent that EMA gains experience with biosimilars, and those applications subsequently come to the US, everyone wins.

Nonetheless, if the US is not to become a secondary market to the EU for biosimilars even after the first cohort of products come off patent (these product's 12 year exclusivity having for the most part already expired, which also means that period of experience with these products in daily clinical use), it will be very important that FDA catch up with EU by optimally using the experience gained in Europe with quality, safe and effective biosimilars, and in the US to date with the originator biologics. This will require the FDA demonstrating a regulatory clarity about their expectations for biogenerics not yet seen by our members, but nonetheless expected. It will necessitate the FDA rapidly learning from the EU guidelines already in existence for biogenerics, as well as with the use in Europe of the biosimilars themselves, and then the Agency making their own expectations clear. This could be through guidance, but most expeditiously through individual sponsor meetings. The processes used in Europe to create their guidances was widely endorsed by many of the stakeholders at the public meeting, but nothing was noted that makes that approach better than the usual FDA procedures for drafting, publishing and revising guidance, or otherwise. And the EU guidelines can already be being considered informally by sponsors for biogenerics as 351(k) BLAs

GPhA notes that the EU statute is different in some key areas from BPCIA, for instance the EU language is silent on interchangeability. Nonetheless, the science in Europe is the same, and the Europeans have been careful in their approval of biosimilars, and none have shown any clinical effects that were unanticipated, nor as discussed at the FDA Public Meeting have any originators formally disputed any of the approvals or the manner by which the biogenerics were approved based on a standard of similarity/comparability. With such a sound record of biosimilars in Europe, GPhA would take it as some measure of FDA's leadership that they find a way that products already shown to be quality, safe and effective to the same level as Europe applies to originator biologics (see Rossignol quote above) can achieve expedited approvals through the new 351(k) biogenerics pathway in the US – this could be facilitated by a guidance on considerations on bridging studies, for instance. If that is not possible, or not in a timely manner, we will have to ask wherein the problem lies, and why patients cannot get access to these products in a realistic timeframe.

GPhA does not support FDA dedicating any resources to deciding that biogenerics to some current 351(a)/future 505(b)(1) products are not possible – the progress in the science and technology make this a wasteful exercise, and while discussed in the statute such an assessment is not required. Timely discussions with sponsors are a more valuable use of limited Agency resources.

³⁹ Reference to finalization of EMA Monoclonal Antibodies Guidelines

As discussed above, GPhA supports all biologics being approved to the same standards and according to the same criteria of quality, safety, purity and potency. Hence, the greatest priority for FDA is to review all applications, whether NDA or BLA, and whether originator or generic/biogenic, to consistent regulatory standards, recognizing that the data will always be case-by-case for any product, and will always be unique to that product and that sponsor in the same manner as is already the case for originator products. Thus, all existing FDA guidelines, including those developed through ICH, that are relevant to any biologic will likely also have relevance to biogenics, and biogenic sponsors are starting from an experience base that was not available to those companies that created the products that will form the biogenic references. Even when biogenics can reference biologic drugs (those products that are biologic in science but that have been approved as drugs under the FD&C Act) 10 years after enactment of BPCIA, there should not be any confusion as to the regulatory standard, and it will be the current approval standard applied to all biologics today.

G. Exclusivity

- 1. In light of the potential transfer of BLAs from one corporate entity to another and the complexities of corporate and business relationships, what factors should the agency consider in determining the types of related entities that may be ineligible for a period of 12-year exclusivity for a subsequent BLA?*
- 2. What factors should the agency consider in determining whether a modification to the structure of the licensed reference biological product results in a change in safety, purity, or potency, such that a subsequent BLA may be eligible for a second 12-year period of marketing exclusivity?*

GPhA did not and does not support the 12 year exclusivity period given to all 351(a) BLAs. The statute is clear that a biogenic/ interchangeable biogenic applications, 351(k) BLA, must be analytically “highly similar” and cannot receive a license until 12 years (plus pediatric 6 months if granted) after the originator was licensed – FDA has no flexibility here. However an alternative biologic, pursued through the current 351(a) BLA route is neither subject to this 12 year exclusivity period, nor to any other aspects of the BPCIA, and can still be filed and approved by the FDA at any time.

GPhA also notes what we believe must be an unintended consequence of the legislation. Namely, any biologic that fails the highly similar standard, can still be approved as a BLA (351(a)), and would then get its own 12 years exclusivity, as well as not be limited by the 12 year exclusivity on any previously approved product (and nor to the cumbersome patent exchange provisions which have not been discussed in this response as they are not a regulatory issue) – this could disincentivize those sponsors most capable technically and scientifically of reaching the “highly similar” requirements of the biogenic pathway pursuing 351(k) applications. GPhA would like to see through FDA implementation, an incentivization of quality biogenic applications through clear and public Agency recognition that achieving the “highly similar” standard allows the Agency to commensurately reduce the preclinical and clinical requirements (just as

occurs when this same standard is applied to sponsors of originator biologics, and in the future sponsors of biogenerics, making manufacturing changes today). This is preferable to FDA merely encouraging “copies” of currently approved biologics to be submitted as BLA’s by requiring all sponsors to complete all the preclinical and clinical studies currently expected for 351(a) applications. That approach clearly disincentivizes bigeneric sponsors, as the slower and more expensive reverse-engineering (even if using Quality-by-Design and other regulatory initiatives aimed at improving product development) and product engineering up front, if it cannot be reasonably anticipated to achieve a reduction in regulatory burden later in development, cannot be justified. Further, for any 351(a) applications, the entire FDA review period can remain secret (as long as it is not reportable as a material matter under the SEC reporting requirements), and the application only becomes public at the point of licensure of the BLA. Any litigation on patents will follow the same court-based process as they do today AFTER the FDA has issued the license and the biologic is marketed. This may further incent some sponsors to file 351(a) BLAs. If companies are to be encouraged to consider the new biogenic pathways, the FDA needs to show how the use of prior knowledge and comparative studies with a US reference product make a 351(k) biogenic application worthy of consideration. Will a 351(k) application be abbreviated or expedited in sum total of time and resources when compared to a 351(a) BLA?

GPhA supports the one year exclusivity for the first interchangeable biogenic given the apparent extra studies required

GPhA does not support 12 years exclusivity for “evergreened” products, but does support clinically relevant improvements as the basis of next generation 351 (a) products from any sponsor. If a new product from the same sponsor as an originator product is submitted then the differences in safety, purity and potency should have sufficient clinical relevance, that such an “evergreened” product offers value to the patient. These products will also each have their own exclusivity from its own original date of licensure, and will not be able to use the new 351(k) pathway. This date will not alter the exclusivity on the first product, which will still be available as a reference product for a biogenic or interchangeable biogenic at 12 years.

We would also like to note that we do not believe that FDA has any statutory authority to disclose applications under 351(k) (indeed no more so than they do under 351(a)). Thus to the extent that biogenic companies and their originator reference product sponsor engage in the patent exchange and litigation process, it is entirely outside of the purview of FDA.

H. Transition Provisions

- 1. What scientific factors should FDA consider in defining and applying “product class” for purposes of determining which applications for biological products may be submitted under the FD&C Act during the 10-year transition period?*

2. *What scientific factors should FDA consider in determining whether another biological product approved under section 351(a) of the PHS Act could serve as the reference product for an application submitted under section 351(k) of the PHS Act?*

There is no definition of “product class” used in BPCIA, and if we look to how it has been used elsewhere a very confused picture emerges. In Europe it has been used for products with single thoroughly characterized active ingredients, such as the somatropins and filgrastims, for entire groups of very different products that share MOA, such as the Erythropoietin Stimulating Agents, and it is now being used for products that simply have a certain commonality of structure as in the case of the monoclonal antibodies. Thus, if FDA chooses to use such a term as “class”, it needs to say how it plans to apply it. Given how the statute is written it may be most widely used to apply to those products that share the same mechanism of action (at the global biochemical pathway level). However, there are many other possible forms of class, and the grouping of biologics in this manner can be useful, especially in the context of regulatory consistency and advice, and possibly but not necessarily guidance. It is not an area where an absolute single definition must apply, but given the extension of the term to other contexts, including those beyond the FDA, it will be important to specify how the FDA is applying “class” whenever they use the term.

GPhA does not support the loss of the Hatch Waxman pathways for any products, and certainly not for biologics drugs before the biogenerics pathways become available. FDA should accept, review and approve ANDAs and 505(b)(2) applications for any reference biologic drug product approved subject to the Federal Food Drug and Cosmetic Act (FD&CA), through March 23, 2020, and also after then for any products remaining as an FD&CA product, including synthetic peptides. It is not apparent that class groupings are relevant for FD&C Act biologic drugs for the next 10 years, since the Hatch-Waxman pathways should continue to apply, and 505(b)(2) and ANDA applications to be reviewed and approved just as they have to date (eight 505(b)(2)s for biologic drugs have been approved, as well as two ANDAs for biologic drugs, and others are under review and the outcomes of these should not be delayed).

Should a sponsor anticipate submitting an application after March 23, 2010 for a 351(k) to a FD&CA biologic drug reference, or even a 351(a) that uses some level of prior knowledge on a 505(b)(1) NDA, then they should be able to discuss its development with the FDA well prior to that date.

Any sponsor should be able to elect to make a biogeneric to any originator 351(a) biologic. It is not up to the FDA to decide *a priori* what is and isn't possible, but the FDA should be able to discuss what data they expect to be necessary to show biosimilarity.

Any biologic approved as a 351(a) BLA today, or in the future, should be presumed to be available as a reference product for a 351(k) application. The variable is the ability of a subsequent sponsor of that 351(k) application to show that they have demonstrated biosimilarity. Thus, while some may believe, and indeed the FDA may concur, that some

products are currently impossible to reproduce independently, the Agency has no need to formalize and articulate that assumption. If the 351(k) sponsor provides sufficiently compelling data that they have achieved the statutory criteria of BPCIA then they should achieve the approval, and if they can't they will receive a disapproval. And as a rough guide, GPhA would suggest that any product on which FDA has approved a comparability based manufacturing change has been shown to be characterizable at a level that allows a manufacturing change without an entire new development program. That makes it a legitimate candidate as a reference for a biogeneric application. There may be others on which comparability has not been used that are also candidates, but the value of consistent standards being applied to all products is that it greatly simplifies the application of a fair and consistent regulatory policy to all sponsors. In sum GPhA supports the freedom for any sponsor to make a biogeneric 351(k) application to any originator 351(a) biologic. It is not up to the FDA to decide *a priori* what it is and isn't possible for a sponsor to make; the Agency's role is to review applications and see if the sponsor has affirmatively demonstrated biosimilarity. Thus, we consider it a distraction to debate whether or not there should be a biogeneric vaccine, or even a biogeneric cell therapy.

I. User Fees

1. *If the existing fee structure under the Prescription Drug User Fee Act (PDUFA) were to be considered as a model in establishing a user fee structure for applications and supplements for proposed biosimilar and interchangeable biological products, what factors and changes should FDA take into consideration, and why?*
2. *What factors should FDA take into account when considering whether to recommend that user fees for biosimilar and interchangeable biological products should also be used to monitor safety after approval?*
3. *In addition, FDA seeks to identify potential participants in any negotiations of user fee programs for biosimilar and interchangeable biological products, specifically companies that would be affected by such a user fee program and industry associations representing such companies. FDA requests that commenter's identify these potential participants by sending to BiosimilarsUserFeeProgram@fda.hhs.gov the following information regarding any company that may be subject to a user fee program for biosimilar and interchangeable biological products, or any industry association representing such companies: The name of the entity; contact person; email address; and a phone number.*

GPhA looks forward to working with the FDA to create a user fee program for biologics that emphasizes safety, access and transparency. This program should also include appropriate metrics that help expedite the availability of biogeneric medicines. Again, we advocate parity and fairness and it is imperative that FDA and industry develop a user fee program that does not create a barrier to entry for biologics. A proactive and safety-driven approach, administered equitably among manufacturers, will

expedite the availability of competitively priced biogenerics while at the same time ensuring that FDA is able to monitor appropriately their development and manufacture. Then, when patients have to choose – brand or biogeneric – they can rest assured that the product is safe and effective according to FDA standards.

To the extent that track and trace obligations need to be integrated, and are applied to all sponsors, this may or may not form part of the user fee discussions. The GPhA inclination is that such considerations need to be addressed separately in order to engage the interested stakeholders for all medicinal products. As such, they should not in any manner detract from biogeneric review and implementation by FDA. Safety considerations should always be raised in appropriate settings and fairly applied to all accountable stakeholders within the necessary organizations. It was clear at the meeting for instance that appropriate data needs to be captured on utilization of all biologics, and much of this is beyond the control of the individual product sponsors. However, as critical members of the supply chain, GPhA members will seek to contribute to the more complete implementation of the current system for all biologics, including biogenerics, than is apparently is the case for originator biologics today. Better data collection can enhance FDA's ability to protect American consumers and please know that the generic industry will support such efforts appropriately. However, revisions to the system will not obviate the need for good data collection, so that must be the most immediate priority. Combined with a proactive and safety-driven approach, FDA can expedite the availability of competitively-priced biogeneric while at the same time ensuring that only high quality, safe, pure and potent products are available to patients. This way, when patients have to choose – originator or biogeneric – they can rest assured that the product is safe and effective according to FDA standards. Consumers demand and deserve the safety, access and transparency that underpin this user fee model, and GPhA will gladly work with FDA to make it a reality.

In conclusion:

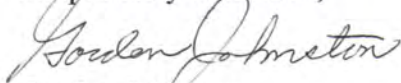
The Biologics Price Competition and Innovation Act was a cautious first step by the US Congress to delegate to FDA the authority to license quality, safe, pure and potent biogenerics. It is now time for FDA to implement biogeneric, and interchangeable biogeneric, pathway in a manner that is predictable and rational to sponsors, and consistent with how the Agency has regulated biologics products to date. Only then can biogeneric sponsors make the necessary investments in a timely manner to bring these products to the US market so that they can be available to the US public and their healthcare providers. GPhA member companies look forward to doing this, and to working with the Agency to ensure that every biogeneric approved by the FDA is as safe, pure and potent as its reference product. The most expeditious way to do this is to apply the basic scientific premises of comparability, even if called highly similar in the context of biogenerics to match the statutory language, as this is a known tried and tested standard with which the FDA and current biologic sponsors have extensive experience. Such consistency is fair, justifiable and allows sponsors to proceed directly in submitting

applications. There are other aspects of the legislation that may cause sponsors to prefer to file the so called full BLA, 351(a), and nothing in the Statute precludes them from doing so.

FDA has the scientific expertise and experience from their prior licensure of the originator to achieve BPCIA's twin goals of price competition and innovation. And, while FDA organizing its own review capabilities, GPhA's members will be planning the development high-quality biogeneric medicines, as well as alternative biologics, at prices that are within the grasp of American patients. Collectively, we have the tools to make this work, just as we did a quarter-century ago for small-molecule drugs under the Hatch-Waxman Act.

We want to thank the FDA for its time and interest in making sure that Americans gain the benefit of the abbreviated biogeneric pathway and ultimately realize great access through meaningful savings on life-saving biological medicines that will be of the same quality, and as safe, pure and potent as their reference products. GPhA hopes that this public process is the start of a dialogue between FDA and stakeholders on these important issues and others critically important to all stakeholders, not least patients.

Respectfully submitted,



Gordon Johnston

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