GPhA
GENERIC PHARMACEUTICAL ASSOCIATION

Division of Dockets Management (HFA-305)
Food and Drug administration
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Submitted electronically to *www.regulations.gov*

Re: Docket Nos. FDA-2011-D-0605; FDA-2011-D-0602; No. FDA-2011-D-0611

April 16, 2012

To whom it may concern:

Thank you for the opportunity to provide the Generic Pharmaceutical Association's (GPhA) point of view on the three FDA guidances outlining the Agency's plans for implementation of the new abbreviated biosimilar pathway created in the Biologics Price Competition and Innovation Act of 2009[1].

We appreciate the draft guidances being published, and recognize the effort that has gone into preparing them. The guidance documents include suggestions for sponsors on a number of regulatory approaches that they can consider, and as such should advance development of biosimilars. The FDA should be commended for proposing these regulatory approaches as part of their implementation of their new statutory authority, including: permitting use of foreign-sourced comparator products; allowing for extrapolation of indications; permitting carve-outs of indications; and allowing for approval of fewer than all routes of administration.

Overall Introduction:
The fundamental premise of the new 351(k) biosimilars pathway is that the new product (biosimilar) can rely on the prior FDA finding of safety, purity and potency for the established, previously licensed product (the reference product). In order to do this the biosimilar sponsor must demonstrate that their product is highly similar to the originator such that this prior FDA finding is relevant as a scientific, regulatory and, therefore, clinical matter. The precise nature of the studies that are required of the biosimilar sponsor are the responsibility of that sponsor to propose and negotiate with the FDA, just as in the case with any other biologic, and will be specific to their particular candidate. Nonetheless, GPhA believes that any sponsor that has demonstrated that their biosimilar has achieved the comparability standard[2], as a scientific

[1] TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition And Innovation (BPCIA) provisions of the Patient Protection and Affordable Care Act (PPACA), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed April 10, 2012).

[2] GPhA is using the definition of comparability as provided in ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed April 11, 2012).

matter, relative to their chosen reference product should have the option of an interchangeability designation at the time of initial approval.

The statutory authority given to the FDA in BPCIA is not proscriptive on the details, and the FDA has the discretion to waive any of the analytical, preclinical and clinical studies described in the statute. We recognize that, in general, the FDA expects to require clinical trials, but such expectation should apply only if and when the totality of the other evidence is insufficient to establish that the proposed biological product is highly similar to the reference product. Underlying the FDA's authority is the expectation that the new regulatory pathway will encourage scientific innovation to create new biologics, as well as support the approval of interchangeable biologics[3] that will compete with current products on which exclusivity has expired. As such, product sponsors, as well as the FDA, can support expeditious biologic development by submitting and requiring only necessary, sufficient and, therefore, actionable data for all biologic products, be they originator (351(a) applications) or biosimilar (351(k) applications) submissions. Further, all stakeholders can be confident in the highly-sensitive modern analytical and functional characterization techniques that all sponsors can apply to identify any differences and to demonstrate that their products are highly similar to another product on which safety, purity and potency has been previously established (intrinsic to FDA licensure). Ultimately, the burden always rests on each individual biosimilar sponsor to demonstrate that its biological product is highly similar to the reference product, and to present the necessary data in their application to FDA. As a scientific concept, this applies for biosimilarity in the same way as it has applied to the comparability exercise in support of manufacturing changes for nearly two decades[4]. These draft guidance documents provide the opportunity for the FDA to reconfirm the Agency's objective scientific standards, and to express confidence in state of the art science and technology available now and anticipated for the future. The Agency can invite sponsors to use the same fair processes that have already developed for originator biologics and thereby encourage the development and review of biosimilars.

GPhA, as the leading representative of those companies that have the capabilities and interest in making biosimilars, has consistently maintained that what matters most to patients, and hence should matter most to other stakeholders, is that all biologics (regardless of whether licensed as an originator or biosimilar product) licensed by the FDA are, and should be, approved to the

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As a procedural matter, this guidance applies only to manufacturing changes made by a sponsor to their own product, but it uses a definition of comparable that applies, as a scientific matter, to any comparison made between two biologics, irrespective of sponsor. The definition of Comparable is "**A conclusion that products have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might contribute to the conclusion**".

[3] Interchangeable biologics include biologics pre and post manufacturing change, whether originally approved as an originator or a biosimilar, as well as biosimilars designated as interchangeable with their reference biologic.

[4] The comparability protocol issued as FDA guidance in 1996 broke with the historical premise, as a regulatory matter, that there is only one process by which any given product can be made; and hence enabled manufacturing change to currently licensed biologics without complete re-development including analytical, functional and clinical studies being necessary. See: 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) April 1996. Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm (accessed April 10, 2012).

same standards of quality, safety, purity and potency. However, while consistency in the standards the FDA applies to all biologics is essential, we recognize that the data in any given application for any product filed to achieve these standards will vary and is at the discretion of the sponsor - data is always case by case. This will apply to biosimilars just as it does to originator products, and this is what currently applies to all drugs (brand and generic), today. The subsequent sponsor, by relying on the FDA's prior finding of safety, purity and potency is not accessing the data of the originator sponsor, and their reliance is only to the same nature and extent as occurs today for generic drugs.

While BPCIA does contain IP and dossier exchange provisions, these are not the responsibility of the FDA to implement. The data in the filings of all product sponsors, originator, generic and biosimilar, with the FDA is always trade secret to that sponsor. Only the FDA gets to see the data in sponsor's applications and, therefore, only the FDA can make the science-based and data-driven judgments on which the patients and their health care providers rely. GPhA and our member companies have confidence that FDA, using the recognized expertise and experience of the Agency's existing reviewers, will make these decisions based on the data presented and irrespective of the business model of the sponsor. There should be no assumption that the medical need for a biosimilar product is less than that for an originator product – this is not a regulatory decision. FDA approval means that the quality of the biosimilar or interchangeable product is no different than that of any other biological product, including the reference product. The "gold standard" of the FDA review and approval process must apply to all biologics licensed in the U.S., so that patients have confidence that any biologic in the market is as safe pure and potent as any other. We have this expectation of the FDA, and we consider it essential that all other stakeholders do as well.

One reservation that we want to express is about the FDA's suggestion that interchangeability is difficult, and the Agency's tendency to talk about higher standards[5] for interchangeability. Given that all biologics and biosimilars must be safe, pure and potent, and that there is therefore a single standard as a legal, scientific and regulatory matter, it is not appropriate to talk in terms "difficulty" and imply a "higher standard" for any subset of biologics. Any Agency suggestion of a "higher standard" for interchangeability will be misconstrued and misinterpreted to mean that any other biological product without such a formal designation is made to a "lower standard". Patients and their providers should not be led to believe that any biological product is of a lower quality than any other biologic, nor confused as to how biosimilars relate to originator biologics. The FDA can and should apply the current same standard for all biologic products - that standard is safety, purity and potency, as the basis of licensure, with quality also the same for all products irrespective for their route to approval.

We also appreciate that these are draft guidances and that the FDA is seeking input from multiple stakeholders. These are not regulations, and no regulations are required by the BPCIA nor are needed to encourage potential sponsors. We recognize that all Agency advice must be adaptable to scientific progress, and is limited in how specific it can become given the range of products, indications and patients involved for biosimilars. Flexibility in the FDA's use of their new

[5] FDA Guidance "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009", Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), published February 2012. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf (accessed April 10, 2012); See page 4, and also in public statements.

authority is essential if the rapidly evolving science is to be optimally captured to expedite the development of these critical products, and likewise for originator biologics which, after all, will be the future pipeline of reference products for biosimilars. Thus, we urge the FDA to exercise caution in adopting detailed guidance on precise approaches, and support the FDA's initial efforts that leave its scientific discretion intact. Consistent application of state-of-the-art science through a series of guidances that can adapt and evolve are in the interests of all stakeholders.

The draft guidances will be useful to aid consistency amongst FDA reviewers, as long as these reviewers also understand that not all studies have to be done for all products. And, just as occurred in Europe[6], some of the guidances will be best developed concurrently with sponsors having meetings with the FDA. This will enable a sharing of the sponsor's experiences and ideas, as well as preliminary data. The FDA can accelerate the US efforts through learning from the appropriate successes of regulators in other highly regulated markets, such as Europe, and harmonizing their efforts in support of global dossiers just as has already occurred for originator products through efforts such as ICH[7].

Given the inherent expense in the development of any biologic, the ability of the FDA to recognize state of the art science, apply it to enhance the quality and availability of all biologics, and yet to minimize any unnecessary studies is important. This will enable patient access to biosimilars, as well as new originator biologics, as expeditiously as possible. Biosimilar sponsors will offer innovation in biomanufacturing and originators have the on-going need to use comparability protocols in support of these manufacturing changes and upgrades. The FDA's openness to rational and data-driven approaches is crucial to all sponsors, and that new techniques replace old ones is likewise essential. Our analytical characterization methods are more developed than they were over a decade ago when the originator product was approved. This is universally accepted, and it is these newer technologies that must now be applied to biosimilars, as well as to any upgrades in manufacturing for the reference products. These same approaches will also be applied to biosimilars in the future when process changes are made using current comparability approaches (just as they have already occurred for biosimilars in other highly regulated markets).

These draft guidances are written for therapeutic protein products. While we understand the reason for that limitation, the scientific and regulatory principles clearly apply to any biosimilar application as well as to any previously approved biologic product. The pathway way continues to be available to any sponsor who wishes to submit an application to any previously approved 351(a) application whether or not it is a therapeutic protein.

Clinical Trials Should Only Be Required and Conducted When Truly Necessary

The FDA often cites Enoxaparin[8] as an example of the types of decisions that the Agency is prepared to make when the appropriate "fingerprint" of data[9] is available. While Enoxaparin

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[6] We cite Europe as a useful source of experience with quality, safe and effective similar biological medicinal products, and not because we are proposing that the FDA implement identical guidelines and development requirements. To the extent that consistent requirements can facilitate global development we believe that their consideration is useful, but duplicative and scientifically unnecessary studies should never be required for any product.

[7] ICH guidelines have been through full notice and comment rulemaking in the US and already apply to biosimilars. See http://www.ich.org (accessed April 11, 2012)

[8] Rachel Sherman Webinar on Biosimilars presented February 3, 2012 available at:

involves a different statutory and regulatory framework from the new biosimilars pathway, and is derived from a previously approved FDA product[10], it is all the more important as an example because the drug product is a naturally-sourced, non-protein, complex sugar mixture that was approved as a fully substitutable (interchangeable) Abbreviated New Drug Application (ANDA). It was approved without any head-to-head clinical studies. For all of these reasons, it supports the GPhA position that clinical trials should only be required when truly necessary – consistent with current science and the BPCI Act. To quote the FDA[11]:

> "Based on our evaluation of all the relevant data and other current relevant scientific information, our experience and expertise, Agency precedent, and applicable law, we find that enoxaparin has been adequately characterized for the purposes of approving naturally sourced generic enoxaparin; and we conclude that an ANDA applicant for enoxaparin can demonstrate active ingredient sameness by meeting five criteria, of which capture different aspects of the active ingredient's"sameness."
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> "In very general terms, 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."

Recognizing the distinctive aspects to this situation with Enoxaparin (most notably that the reference product was approved as a drug in 1993, and also that it is naturally sourced), as a scientific matter the issues are fundamentally about characterization and the removal of residual uncertainty when the product is being made by a different sponsor. While the characterization methods and criteria may differ for each biologic, the approach of the sponsor establishing a framework for product understanding, and then reducing residual uncertainty, involves similar regulatory science considerations for any biologic. Hence we concur with senior Agency officials referring to their experience with Enoxaparin as being pertinent experience for developing scientific review capabilities, as well as an example of a flexible approach, for the Agency's future evaluation of biosimilars. Likewise for the other ten biologics drugs approved as ANDA's or 505(b)(2)s[12], that each refer to a previously approved 505(b)(1) biologic drug as integral to their approval. And indeed most of these (seven of the eleven) were also naturally

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https://collaboration.fda.gov/p93059689/?launcher=false&fcsContent=true&pbMode=normal (accessed April 9, 2012)

[9] FDA Press release http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2010/ucm220092.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=FDA Enoxaparin citizen petition response&utm_content=4 (accessed April 6, 2012); FDA Citizen Petition response on Enoxaparin, available at: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM220083.pdf (accessed April 6, 2012).

[10] Heparin is a USP monograph compliant product – see http://www.usp.org/usp-nf/hot-topics/heparin (accessed April 9, 2012).

[11] FDA response to the Aventis citizen petition, Docket No. FDA-2003-P-0273. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM220083.pdf (accessed April 11, 2012).

[12] For list of all 11 products see Table 1, McCamish, M and Woollett, G "The State of the Art in the Development of Biosimilars", Clinical Pharmacology and Therapeutics, Nature's Clinical Pharmacology & Therapeutics, Regulatory Issue, (March 2012); **91** 3, 405-417. Available at: http://www.nature.com/clpt/journal/v91/n3/full/clpt2011343a.html (accessed March 29, 2012).

sourced products, and only one was recombinant reference and recombinant follow on approved to the standard of "highly similar". Nonetheless, in all cases the FDA made a scientific evaluation of the available data, requiring appropriate preclinical and clinical studies where necessary and admissible (possible for 505(b)(2) applications as a regulatory matter, but not for 505(j) ANDA applications), and there have been no unusual or unexpected adverse events with any of these products once marketed. Nothing has been shown or attributed to lack of sameness for any of these products. Just like these complex and naturally-sourced biologic drugs, as the FDA has previously articulated[13], and as also discussed in the draft guidances, a biosimilar approval will be based on the totality of the evidence available to the FDA on the product. This is the data as submitted by the biosimilar sponsor comparing their product and the originator. This begins with physical, chemical and functional characterization data to demonstrate highly similar product critical quality attributes, and then confirmatory animal and clinical studies as needed. The Agency's previous experience with originator products (specifically and collectively but not accessing the application of the originator), as well as with biologic drugs, shows that the FDA is well qualified to make appropriate and data-driven decisions for biosimilars. The main distinction for biosimilars, as opposed to the biologic drugs such as Enoxaparin, is that they will refer to a reference product that happened to have been approved under the PHS Act as a 351(a) BLA rather than as a FD&CA 505(b)(1) drug[14].

The FDA has publicly recognized on many occasions[15] that the resolution and fidelity of analytical studies can be much greater than that possible with in vivo studies in either animals or even in clinical trials in human subjects. Thus, the relevance of animal studies can be limited, but in cases where they are useful, they can be considered and should be included. However, just as is the case for all products, animal use should be minimized where it does not contribute necessary and, therefore, actionable information.

Clinical studies for biosimilars, in particular, are not straightforward to conduct as a scientific matter, and the ethical considerations will be particularly complex. The FDA has said that they do not intend to require unnecessary studies as this would be unethical,[16] and GPhA strongly supports this position (indeed supports it as applying to any analytical, functional or clinical study for a biosimilar, not just to clinical studies). The draft guidances contain many interesting scientific ideas, but we would not expect that many of these studies would routinely be required for all biosimilars. In particular suggestions on choosing sensitive sub-therapeutic doses as a way to find clinical differences may not have a sound rationale. By definition these cannot identify clinically meaningful differences, as required in the statute, and will likely be unethical.

The expectation that clinical studies for biosimilars will provide more than confirmatory information is very low[17]. Hence, they would be done to show that the outcome is as expected and to reassure all stakeholders, and ultimately consumers, that the biosimilar is indeed as safe, pure and potent as the previously assembled analytical data already has indicated. Given this

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[13] Kozlowski, S., Woodcock, J., Midthun, K. & Sherman, R.B. Developing the nation's biosimilars program. New Engl. J. Med. **365**, 385–388 (2011).

[14] In Mar2020, biologic drugs that were approved as 505(b)(1) NDAs will also become available as reference products for biosimilars, but again the science will be the same.

[15] John Jenkins at DIA 2011, Janet Woodcock at ICD2 Barton Creek 2012.

[16] Rachel Sherman said at the biosimilars session at BIO201, also BioCentury TV http://www.biocenturytv.com/player/1475583154001 (accessed April 11, 2012).

[17] Temple, R. "A regulators view of CER", Clinical Trials (2011) **0**: 1–10.

limitation on the ability of the clinical studies to provide meaningful information, the clinical trial designs and what can be learned from them is critical to consider. The FDA should not require any clinical studies that will not inform subsequent FDA determinations on the license or use of the biosimilar. That is, clinical trials for biosimilars must provide actionable data that is necessary for approval in order to be required. When a manufacturer makes a manufacturing change to the currently approved biologic using comparability regulatory procedures[18] (and as will occur for biosimilars and reference products alike in the future) animal and clinical studies are frequently avoided. Similar tools will likewise be available for use by applicants in demonstrating a biosimilar is "highly similar" based on non-clinical data. Dr. Woodcock testified in 2007 that less in 1/50-1/100 times is any clinical data required when comparability is used[19], and this provides important context for how we should be considering clinical studies for biosimilarity – regulatory caution may be valid, regulatory disparity is not.

The statute allows biosimilar sponsors to be selective in the conditions of use (indications) and routes of administration that they pursue, and while they must provide data to support those that they want to claim, they should not be obligated to provide data on those that they are not planning to seek, nor should any interchangeable biologic be labeled for those aspects of the originator product that have NOT been sought by their sponsor (this includes both indications and a formal designation of interchangeability). This has never been the case for other products approved by the FDA, and should not be the case for biosimilars. Indeed the closest parallels, the biologics drugs cited above, are again apposite - none of the 505(b)(2) biologic drugs are labeled as NOT interchangeable with their reference product, and in those instances where the product did not have all the indications of their reference at the time of initial approval they did not carry information as to the indications for which they were NOT approved. These issues are addressed to some extent in the draft guidances[20], but some of the consequences of efforts to seek extrapolation are not clear. In particular the opportunities to seek interchangeability for only a subset of the conditions of use of the originator product is not clearly stated and yet would seem to be possible under BPCIA, as a legal matter. There is no value in involving the FDA in patent conflicts that could involve particular indications, presentations or formulations, as this would only deflect resources away from the agency's extensive responsibilities to review and approve products. The law permits flexibility to carve out indications and the FDA should be clear on this point to promote the early use of the biosimilars pathway.

For the extrapolation of data between indications, the burden is on the biosimilar sponsor to show that the mechanism of action (MOA) (recognizing that there may be more than one MOA in the case of some multi-domain proteins) for the different indications of the originator that they wish to achieve for their biosimilar are the same. However, with appropriate scientific data developed in a stepwise manner, an applicant should be able to show, as was the case with Enoxaparin, that the product is a highly similar, interchangeable biologic. The value of clinical studies for any indication must be evaluated carefully and limited to those indications where clinical testing is necessary. That such extrapolation is appropriate without clinical studies is well

[18] ICH Q5E – comparable is defined as "highly similar quality attributes," and "highly similar" is the standard in BPCIA.

[19] Q&A following testimony: Follow-on Protein Products. Statement of Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer Food and Drug Administration before the House Committee on Oversight and Government Reform, March 26, 2007, and question and answer session. http://www.fda.gov/NewsEvents/Testimony/ucm154070.htm (accessed April 11, 2011).

[20] No. FDA-2011-D-0611, Draft Guidance for Industry on Biosimilars: Questions and Answers: I.5,6,7.

established through the nearly two decades of use of the "highly similar" analytical standard in support of manufacturing changes, where MOA has never been an issue, including on the very same products that will be the reference products for biosimilars. It is not possible, as a scientific matter, that an analytically highly similar biologic will not function by the same MOA or MOA(s) as their reference product[21]. Where an applicant has been through a stepwise development approach, provided a submission wherein the totality of the evidence indicates that a biosimilar has the same MOA(s), then the indications covered by that MOA(s) must be approved. We recognize, as a statutory matter, that MOA has been raised in BPCIA and, therefore, the FDA must consider it as a regulatory issue during implementation. We request that the Agency consider it as an opportunity for regulatory consistency with other biologics (both at their initial approval and also during the use of comparability protocols in support of manufacturing changes) given the extensive authority that the Agency has appropriately been given in the statute to determine what studies are needed and to waive all unnecessary studies. For these same scientific reasons, mandating pediatric development across-the-board for biosimilars is inappropriate, and waivers should be issued.

In summary, the biosimilar sponsor chooses the indications, formulation, route of administration, etc., that they are seeking for their biosimilar candidate product and then must provide the data to support these requests. They are limited to being a subset or the whole set of the reference product and, for instance, cannot get a new indication not held by the reference product, but those which they pursue are entirely within the discretion of the biosimilar sponsor. And as a general rule, the biosimilar sponsor should not be expected to provide greater data than was provided by the originator as the basis of their original approval – so for instance on extrapolation between indications comparable receptor binding should suffice and downstream intracellular pathway elucidation not needed to show that the MOA is the same. Likewise for interchangeability, methods used and the data submitted in the application should be at the discretion of the sponsor, and no greater scientific requirements should apply to a biosimilar than apply to a biologic making a manufacturing change (recognizing that data requirements will always be case by case).The FDA has the authority to consider the data and grant interchangeability when the statutory requirements are met.

While the value of the historical data is evident, the connection of the post-change biologic to the pre-change biologic, and hence the validity of the prior finding of safety, purity and potency presents the same scientific challenge. Only if high similarity is established can that bridge be built, and likewise if that same high similarity is established for a biosimilar, so the hypothesis of sameness can be equally confidently asserted. A biosimilar can be as similar to its reference as the reference is to itself over its lifetime, and the FDA can have equal confidence in the data irrespective of the sponsor's business model. Put another way, the FDA cannot assume what is unknown/unmeasured about an originator product is the SAME pre and post manufacturing change, and what is unknown/unmeasured about an biosimilar versus its reference is DIFFERENT. This is not the Agency applying a consistent standard to all biologics. And clinical trials will not compensate for any inconsistency in analytical data.

The theme of consistency and fairness in the FDA's implementation of regulatory requirements will be crucial to the ultimate confidence in the quality safety, purity and potency of biosimilars.

[21] Such a requirement is not included ICH Q5E the guidance covering a manufacturing change using comparability, but is imposed here as a statutory matter in BPCIA.

The rapid progress in the science can and should be accommodated, and this can be done independently of the regulatory pathway, originator or biosimilar, to which it is being applied. The guidances as written are suggestive of a difference in data burdens for originator and biosimilar sponsors, and in some cases explicit as to the difference in standards to be applied. GPhA cannot support such a discrepancy as being in the interest of any stakeholder.

Immunogenicity and Biosimilars

Immunogenicity is fundamental to the value of some biologics (e.g. vaccines), of concern for other biologics (e.g. Epoetin alfa), not an issue for others (e.g. Filgrastim), but must always be considered for all biologics. It will also always be the greatest concern for those products that are being administered as replacements for endogenous proteins, as a cross reaction in those instances is potentially the most dangerous for the patient. And biologics representing these endogenous proteins were the earliest approved recombinant products since we began using biotechnology as a means to manufacture what we had previously sourced from animals, including humans (e.g. insulin, human growth hormone). Only later has the biopharma industry introduced products that are "designer" and that don't have endogenous counterparts (e.g. Etanercept). Even monoclonal antibodies are essentially naturally sourced products (originally mouse, later chimeric, and then humanized and human), albeit biosimilars to them will be recombinant, but in both instance carry lower risks even were immunologic reactions to them to occur.

In general, biologics, including biotech products, have an excellent safety record, and the toxicity concerns of small molecule drugs do not occur in the same manner. Administration can be more of a challenge as virtually all are injected products, and only a few are self-administered. The escalation in safety concerns arose just as the potential for biosimilars became a reality. Thus biosimilars were framed in terms of presumptive risk of creating immunogenicity reactions, even though by definition any "evidence" of a problem with immunogenicity had to be with originator products, since no biosimilars has yet been approved. And even now there have been no unusual or unexpected adverse events reported with marketed biosimilars in any country (and we suspect that a lot of studies looking for differences have been done given the determination amongst some stakeholders to find problems, but none are published[22]). Thus, even years after 14 biosimilar products have been approved in Europe, and millions of patients have been treated with these products worldwide, the most commonly cited example of a dangerous immunogenic response to a biologic is still the association of Pure Red Cell Aplasia (PRCA) with particular batches of Eprex© (Epoetin Alfa) used a decade ago. PRCA is seen with a number of ESA's, but the 25 fold increase of incidences to 4 in 10,000 at its peak occurred largely in Europe where it was ultimately correlated with a manufacturing change to remove Human Serum Albumin (HSA) due to the hypothetical risk of TSE[23]. Some deaths resulted. The scientific debates continue to this day as to the exact cause, but aggregation of protein was induced and is clearly a proximate cause for the increased immunogenicity. Aggregation is now a parameter examined

[22] A lot of aspersions are cast, but we have seen no reports from credible sources or papers in the professional and scientific literature that show any quality, safety or efficacy issues with products approved as biosimilars (based on head to head comparability) in any highly regulated market.

[23] This was the height of the Mad Cow Disease or Bovine Spongiform Encephalopathy (BSE) scare in Europe when the supposition was made than any of the Transmissible Spongiform Encephalopathies (TSEs) could be transmitted by animal sourced materials. It provides a superb example of the maxim that "To replace something of known but infinitesimally small risk with something of unknown risk is not to make a product safer."

for all biologics. Such collective learning as to what can make some products have increased immunogenicity has value for originator sponsors and biosimilar sponsors of more than just Epoetin alfa in the future. However, it is also important to note that the incidence of PRCA was always extremely low, and at a level that cannot be known for any product at the point of its initial approval – not for an originator and not for a biosimilar, and not for an interchangeable biologic after a manufacturing change. However aggregation can be examined for all batches of all biologics and this is now required by regulators.

While the overall risks of immunogenicity with originator products are low and the examples are even rarer, it must be recognized that the risk of unanticipated immunogenicity reactions with biosimilars will always be less than with truly innovative biologics. This is because the biosimilar will always be informed by what has been learned in the context of decades of use with the originator product, and because the "highly similar" analytical demonstration by the biosimilar sponsor will significantly reduce the probability of a difference being seen clinically (albeit never to zero). This is particularly the case of the potential for immunogenicity to the active moiety, but will also be true of the manufacturing systems such as, antibody responses to host cell proteins. Nonetheless, it is the immunogenicity of the active moiety than raises the issues of loss of efficacy after repeated doses, and, because of the possibility for an immunological cross reaction with endogenous proteins, this is of particular concern for replacement proteins (those proteins that the patient has an insufficiency of and that are the basis of their disease or symptoms – especially true of some of the orphan diseases). Potential immunogenicity is also the presumptive basis for the BPCIA's requirement for the additional demonstration of the absence of safety and efficacy concerns with switching interchangeable biologics[24]. However, there is no scientific basis for this concern[25], and these are studies that the FDA may not need to require unless there is a specific anticipated value and meaning to the data.

Just as is the case with manufacturing changes using comparability procedures, it may not be possible to definitively show that immunogenicity responses will not be a problem in some patients. Careful use and monitoring for all biologics is important. The Eprex© (Epoetin alfa) example also taught us that good records must be kept on every product throughout its use, and that this includes the batch number. However, biosimilars and other, newer biologics developed using modern current state of the art characterization and quality by design methods may reduce the risks of immunogenicity compared to the older reference biologics. Reasonable post market surveillance requirements will best serve all stakeholders, and are another instance where consistent regulatory requirements are appropriate for all biologics.

In summary, all FDA approvals are based on a risk/benefit assessment that the likelihood of a clinically meaningful immunological response is low. In the case of a biosimilar an immunological response to the protein is no more likely than with an originator product, and indeed a case can be made that it is less likely. Given the progress made over the last few decades with biomanufacturing there is a likelihood that biosimilars can be made more

[24] While the BPCIA does not require switching studies per se, it does require that sponsors demonstrate no change in risk (safety or diminished efficacy) for the patient if they are switched between the originator and the reference product. and the biosimilar. This is not based in a sound immunological hypothesis and switching does not increase the risk of an immunological response, but it is a statutory requirement.

[25] We are not aware of any study that shows that it is the switching between two proteins that leads to an increase in immunogenicity and would welcome anyone who has such an example sharing it with the broader community through a publication in the peer reviewed scientific literature.

consistently and with higher purity than was possible for their originator counterparts, but the concern is that they show no greater immunogenicity – not that they show less immunogenicity. That this will be possible through analytics and the demonstration of "high similarity", plus the lack of feasibility (ethically, through patient availability, and economically) of the massive clinical studies, will be important to recognize and discuss amongst all stakeholders. This is already the conclusion today when comparability standard is applied to support manufacturing changes for currently approved biologics and immunogenicity studies are rarely if ever required).

It is important to note throughout that the "absence of clinically meaningful differences" as required in BPCIA, does not mean the absence of any clinical differences, and even more importantly that the "absence of clinically meaningful differences" need not be demonstrated only through clinical data[26]. Were that so, the value of any of the characterization development steps would be questionable. It is important that applicants have the innovation incentive to develop approaches that can demonstrate the absence of clinically meaningful differences without the use of clinical trials; a practice that is well-established today for generic drugs.

A Biosimilar Should Be Tracked Uniquely but a Unique USAN/INN Would Create Safety Problems

Many of the issues that have been raised in the content of the biosimilars debate apply to all biologics, and in some cases even to all medicinal products regulated by the FDA. One such instance is the issue of the generic or nonproprietary or established name, where the implications for any change by the FDA would ricochet around the world given that the current naming system is global. The naming conventions for the active ingredients in medicines as established over 50 years ago under the joint agreement of some 197 countries, administered by WHO[27]. The purpose of the INN is one to which the global community has committed and in which the FDA has led, and in the vast majority of cases the USAN matches the INN. The role of the INN is as below:

> "Guidance:
> International Nonproprietary Names (INN) facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A nonproprietary name is also known as a generic name.
>
> Mandate:
> WHO has a constitutional mandate to "develop, establish and promote international standards with respect to biological, pharmaceutical and similar products.
> The World Health Organization collaborates closely with INN experts and national nomenclature committees to select a single name of worldwide acceptability for each active substance that is to be marketed as a pharmaceutical. To avoid confusion, which

[26] ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed April 10, 2012).

[27] WHO International Nonproprietary Names (INN) Home page. Available at: http://www.who.int/medicines/services/inn/en/.

could jeopardize the safety of patients, trade-marks should neither be derived from INNs nor contain common stems used in INNs."

FDA has previously submitted a thoughtful and carefully written paper to WHO on the naming of biosimilars, and given that this paper is no longer available on the FDA website, we have attached a copy to this docket submission for the convenience of all stakeholders[28]. In this document, FDA is clear that the Agency supports the INN's original purpose, and that the INN is neither the sole basis for prescribing nor the premise for interchangeability. Indeed the INN reflects the active ingredient only and is not the product (it does not reflect dose, formulation, route of administration etc., all of which must be specified by the prescriber). It is but one element on a product label, developed to inform prescribers worldwide as to the active moiety in medicinal products for their consideration during clinical use. This is important and a view with which GPhA concurs. To destroy the INN system, and lose its worldwide value, due to the failure of complete data collection for some originator products in the past having led to difficulties in track and trace with those same originator products[29] would not be good public health policy.

We agree with the FDA:

> "Specifically, INNs should not be used to imply pharmacologic interchangeability of products with the same active ingredient(s) when no credible scientific data exist that demonstrate such. Likewise, INNs should not be used to differentiate products with the same active ingredient(s) when credible scientific data demonstrate that no pharmacologically relevant differences exist."

The INN is not the sole basis for prescribing in the US, but it does nonetheless help inform health care providers as to the active ingredient in medicines, including biologics, and will help prevent double-dosing in the case of the biosimilars IF the biosimilar shares the INN with its reference product. GPhA, and all our members, strongly believe that to impose different INNs on biosimilar sponsors would create unique safety problem as physicians and other health care providers have every reason to expect that products that share active ingredients will share INNs, and so different INNs mean different active ingredients. This is what is occurring in the other highly regulated markets and there have been no instances of confusion. Indeed, even in the US, originator biologics that have never been compared in head to head studies share INNs and there have been no plans made to change these INNs due to the perception of, or an actual safety problem. We assume that if FDA was to impose unique INNs on biosimilars there would also be plans made to rename all other biologics that share INNs, most especially those that have never been compared to establish a data driven substantiation of "sameness".

We also recognize that part of the concern with the INN for some stakeholders is to force a biosimilar to have a different INN/USAN in order to preclude the ready substitution of the biosimilar for its reference at the state level. This could occur even when the biosimilar is labeled

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[28] FDA Paper submitted to WHO September 2006. "US FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars. September 1, 2006" attached to this submission.

[29] Eprex in EU being the case in point - Casadevall N. Immune-response and adverse reactions: PRCA case example. http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500011064.pdf (accessed October 12, 2011).

as interchangeable with its reference product. That most state laws do require products to share USANs in order for substitution to occur is appropriate given that this matches the intent of the INN. It would be unfortunate, however, if this value of the USAN was to be obviated in order to preclude the full contribution to the public health of biosimilars in the manner that we have become used to expecting for generic drugs.

We would like to highlight the distinction between any system to be employed for the monitoring of the utilization of products, and the data collection that is required to ensure that that system works effectively. This may be where some of the confusion has been coming from for some stakeholders as there has been a lack of specificity in the discussions to date. That there have, apparently, been occasional instances of incomplete record keeping for some originator biologics, and other products, in the US, is not a valid basis for proposing an entirely new system to track biosimilars (which by definition have not been the products mis-tracked as none are yet approved in the US). Yet again problems with a few originator products are being used to pre-suppose problems for biosimilars – this is not appropriate at any level. It would be better to examine whether the failures in the current system have occurred and how they can be addressed. Then the lessons learned can be applied to all products in the future. This would be an appropriate form of the iteration and learning that Dr. Woodcock has already proposed for the review process itself[30]. Further, were any new systems or elements to be proposed to replace current system, these would also be needed to be examined for their ability to create other problems through the loss of key capability of the current system. That would not be a trivial undertaking.

The current systems in use in the US do not require a unique INN/USAN for effective track and trace of products. Given our dispersed systems, absent a single payer, much of the track and trace of products is related to the reimbursement system and relies on the NDC number.

Affordability and Access Is Optimized by Global Dossiers for All Biologics

Global dossiers are the norm for originator biologics, and in many cases the product approved in each of the highly regulated markets is identical. In some instances the formulations vary, and in other cases there are minor differences in the dosing and devices. However, as a scientific matter, the drug substance is usually identical, generated in the same cell line and often produced in a single facility for worldwide distribution.

BUT, as a legal matter, the originator product is defined by the label on the tube, and not by its contents. Thus a US labeled product is the 351(a) reference product required in the statute, and that same product labeled for, say, European use is not. The European label makes it a European product suitable as a reference product for a filing in the EC, but not the US. This is what creates the so called reference product problem.

GPhA supports the appropriate use of data generated in head to head studies with foreign-sourced comparator product as long as it is scientifically justified. Likewise, we concur that the unnecessary, and therefore unethical repetition of any studies, but most particularly clinical studies, should not be required by the FDA as the basis for the approval of a biosimilar in the

[30] Woodcock J. "Evidence vs. Access: Can Twenty-First-Century Drug Regulation Refine the Tradeoff". Clinical Pharmacology & Therapeutics (2012) **91** 3, 378–380. Available at: http://usrexp-sandbox.nature.com/clpt/journal/v91/n3/full/clpt2011337a.html (Accessed 10 April 2012).

US. This means that public information that a single facility produces the product, and appropriate characterization data confirming the match should suffice for bridging studies with the foreign-sourced reference product to a US biosimilar application. Three arm clinical trials of EU reference, US reference and a potential biosimilar are clearly scientifically unnecessary and therefore clinically inappropriate, and inevitably unethical. These are also incompatible with the totality-based-evidence that the FDA is strongly supporting and advocating through the draft guidances.

The EU is concurrently addressing the reference sourcing issue, but it is more immediately faced in the U.S. by the FDA because the statutory authority enabling biosimilars that the EMA gained in 2004 did not come to the FDA until 2010. Thus, a number of biosimilars have already been approved in Europe and their sponsors should be able to access the US market with these already proven quality, safe and effective products, and the question is whether they are expected to repeat extremely expensive clinical studies for purely confirmatory study results. We do not believe that the FDA would disagree with this conclusion as a scientific matter. The barrier to entry represented by the expense of repeated these scientifically and clinically unnecessary studies cannot be under-stated, estimates run to $100 million purely for the purchase of the reference product (and some originators are apparently not willing to sell the US sourced reference product for clinical studies for biosimilars on the premise that it is not for treatment). Sponsors who have had meetings with the FDA, especially prior to the issuance of the three guidances, have run into a high level of regulatory caution even for those products that can essentially be shown to be identical through analytics (for instance, those products with no post-translational modifications, such as filgrastim, are essentially big chemicals and are vastly simpler than the oft-cited example of Enoxaparin which was approved as a fully substitutable generic drug with no clinical studies by FDA).

GPhA would like to encourage the FDA to ensure that reviewer education, and most especially the education of the clinical reviewers who have had considerably less experience with comparability procedures than the CMC reviewers (who routinely handle comparability protocols), be given priority as part of the overall FDA to ensure consistency through the BIC and other internal committees. Through no ill intent, clinical reviewers approach every question with a clinical trial as the solution, and will have had no reason to be aware of the full nature and extent of the use of comparability procedures with these complex biologics over the last decades. Indeed any product on which comparability procedures have been used, and for which full clinical trials have not been required, is a demonstration of the suitability of that biologic as a reference product for a biosimilar without a complete clinical development program. This is regulatory consistency in the application of science-based and data-driven standards.

Americans Can Trust FDA's Approval of Biosimilars as Safe, Pure and Potent If the FDA Commits To Applying The Same Standard To All Biologics

The FDA has been clear that a biosimilar sponsor has to substantiate the relevance of the safety, purity and potency of the originator to their biosimilar candidate. Then, just like the originator connects all the way back to their own original approval every time they apply comparability approaches, so the biosimilar can also rely on that prior finding of safety, purity and potency. For both products the bridge is ALWAYS back to the date on which the originator was first approved in the US. The originator is always interchangeable with itself over its lifetime, and the biosimilar can be designated as such if its sponsor provides sufficient data to support such a designation. The choice of the label they pursue is always a sponsor's choice.

The statute gave the responsibility for reviewing biosimilar applications to the same review divisions that have responsibility for the originator products. This is a further reason for all stakeholders to be assured that consistent standards will be applied by the FDA to both originator and biosimilar biologic products. While the FDA has been reorganized and recombinant products were moved from CBER to CDER in 2003, the reviewers moved along with the responsibilities, and these divisions have the necessary expertise, and experience as well as the on-going oversight of, the reference product. To have consistency in the review standards, and to have overlap in the use of expert and experienced reviewers will provide the greatest assurance possible for patients and their health care providers that biosimilars are indeed as safe, pure and potent as any other biologic licensed by the FDA.

The details and careful consideration in these guidances, and the absence of open encouragement for biosimilar applications, is indicative of the FDA's regulatory caution. GPhA suggests that the FDA can have greater confidence in their prior experience, and on-going oversight with nearly 150 approved (FD&CA) and licensed (PHSA) recombinant products, and that the Agency is in a position to support the application of biosimilars today.

Collaborating With FDA In Support Of Biosimilar Development

GPhA and its members look forward to continuing to work with the FDA to make biosimilars available to patients. As the Agency moves forward, GPhA believes it is important to underscore the importance of streamlining the process of interactions between biosimilar sponsors and the Agency. The FDA has committed to an extensive and intensive process to ensure consistency in the Agency's regulatory procedures by having four internal meetings prior to each meeting with a biosimilar sponsor. While GPhA appreciates the intent of this internal Agency effort, it should not come at the expense of timeliness. If the GPhA-supported user fees for biosimilars are to enable the FDA to meet the performance goals that are essential to all stakeholders to ensure access to these critical medications, then the FDA must ensure that all the pre-approval development meetings with sponsors occur in a manner concordant with industry-wide product-development schedules. Otherwise, the meet "early and often" concept encouraged by the Agency will become a hindrance to access rather than a facilitator of access.

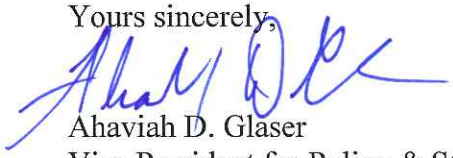
In Conclusion:

By definition, through having been approved as a biosimilar, the biosimilar sponsor will have shown that the entirety of the originator safety database is as relevant to the biosimilar as it is to the reference product. Thus the biosimilar will be supported by a much greater safety data set of its first day of approval that can ever apply to any originator product on its first day of approval – indeed at least 12 years of post-approval data in addition to preapproval data, including immunogenicity data will be relevant to that biosimilar. This will support the safe use of the newly approved biosimilar product – an advantage that could not be claimed by the original reference product. The truly innovative product will always be the one we know least about on its first day of approval, but the ability to offer new therapeutic options will warrant that risk. The biosimilar will be made to the same quality, be as safe, pure and potent and its value will be affordability and access – both unmet public health needs in their own right. Further, GPhA believes that any sponsor that has demonstrated that their biosimilar has achieved the comparability standard, as a scientific matter, relative to their chosen reference product should have the option of an interchangeability designation at the time of initial approval.

GPhA has confidence in the FDA, and we believe the Agency is ready to review and approve biosimilars today, just as they already routinely approve interchangeable biologics after manufacturing changes based on very limited data sets. Thorough but expeditious reviews of biosimilars are best achieved by the Agency publicly committing to apply their expertise and experience and consistent standards to all biologics. By so doing, the Agency can encourage biosimilar applications to be submitted. Without such submissions the FDA cannot review and approve biosimilars, and patients cannot benefit. And without a clear commitment to consistent standards, an environment of such clear regulatory uncertainty exists such that sponsors are not sure the new 351(k) pathways are feasible. Most critical of all is clarity that unnecessary clinical studies will not be required by the FDA unless the data produced would be meaningful and absolutely necessary to ensure that only high quality; safe, pure and potent biosimilars are marketed.

If you have any questions regarding these comments, please contact me at aglaser@gphaonline.org or (202) 249-7110.

Yours sincerely,



Ahaviah D. Glaser
Vice President for Policy & Strategic Alliances

Attachment 1

U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars

September 1, 2006

Support of INN's Orginal Purpose

The United States Food and Drug Administration (U.S. FDA) continues to support the original purposes, premises, and uses of the INN and believes the system has provided many positive elements to the world's public health, especially in facilitating the exchange of scientific data and reports on various products with the same active ingredient(s).

The USA recognizes the INN system as a cataloging system whereby many products worldwide may share the same internationally recognized nonproprietary name based on drug substance. In this manner, the INN system provides a clear mechanism to health care professionals worldwide for identifying medicines and communicating unambiguously about them based on pharmacological class.

The U.S. FDA's concerns in today's discussion are (a) that the INN not be used in ways that could jeopardize the health of patients, and (b) that we not unnecessarily institute changes that could jeopardize the public health benefits of the present INN system.

Specifically, INNs should not be used to imply pharmacologic interchangeability of products with the same active ingredient(s) when no credible scientific data exist that demonstrate such. Likewise, INNs should not be used to differentiate products with the same active ingredient(s) when credible scientific data demonstrate that no pharmacologically relevant differences exist.

Pharmacologic Interchangeability

"Interchangeability" is a term used for purposes of this discussion to designate the situation where scientific data convincingly demonstrates that two products with very similar molecular compositions or active ingredient(s) can be safely substituted for one another and have the same biologic response and not create adverse health outcomes, e.g., generation of a pathologic immune response.

With small molecular products, there is a long history to support the use of various scientific approaches to establishing "bioequivalence" between products with the same active ingredient(s) produced by different manufacturers. We know now that these "bioequivalent" products can indeed be expected to behave in a pharmacologically interchangeable manner when used in patient care.

With protein products, as of today, the FDA has not determined how interchangeability can be established for complex proteins.

Different large protein products, with similar molecular composition may behave differently in people and substitution of one for another may result in serious health outcomes, e.g., generation of a pathologic immune response

When scientific data establishing pharmacologic interchangeability do not exist, especially with more complicated protein molecules with potential critical immunologic safety issues, it is important that patients and physicians be aware that protein products with similar molecular composition may indeed not be interchangeable.

U.S. FDA believes that the only way to establish pharmacologic interchangeability is through scientific data, and nomenclature should not be used as a way to imply such when there are not credible supporting data.

Situation in the United States of America

Product Dispensing

To date, the USA does not use non-proprietary names as a vehicle for communicating pharmacologic interchangeability. There are examples in both small molecule products and more complex proteins of products having the same non-proprietary name and there not being scientific data establishing the interchangeability of the products. For example, multiple innovator products containing interferon β-1a, insulin, or somatropin share the same non-proprietary name and there are not scientific data that support the pharmacologic interchangeability of these products.

In the USA there are recognized mechanisms in place other than non-proprietary names for assigning pharmacologic interchangeability: e.g., equivalence ratings in the Orange Book; specific labeling regarding pharmacologic interchangeability.

In addition, in the USA, there are drug dispensing systematic "checks" to help assure appropriate dispensing of products based on whether or not there are scientific data establishing interchangeability. However, this might not be true in other countries.

Because of the many alternative mechanisms in the U.S. for preventing inappropriate substitution, at this time the U.S. FDA does not consider the proposed change to the INN policy for naming biosimilars to be necessary to prevent inappropriate substitution in the United States. Appropriate prescribing and dispensing practices in the U.S. encompass more than just conveyance of a drug name from prescriber to pharmacist. Regulations concerning drug substitution by pharmacists vary from state to state in the United States. However, there is always a mechanism by which the prescriber can authorize that the brand or innovator product be dispensed. As an additional safeguard, many states utilize a state drug formulary that includes listings of drugs with the "same" active ingredient(s) considered to be pharmacologically interchangeable. Even if two biosimilars would have the same nonproprietary name, they would only be included on a list of interchangeable products, if there were scientific data to justify such. Thus, a common INN in itself does not imply or warrant inclusion on a state's list of interchangeable drugs. The FDA recognizes that the authorized prescribing information represents the most important means of communicating information about an authorized product to prescribers and pharmacists. The authorized prescribing information should

distinguish a product from others considered to be biosimilar if indeed there is not data to substantiate pharmacologic interchangeability. In addition, the role of continuing professional education about interchangeability risks with biosimilars should be further emphasized.

The issue of interchangeability is not an issue of nomenclature but a scientific question that needs to be decided on its own merit. The question of nomenclature is more relevant to concerns about pharmacovigilance and the prevention of inappropriate substitution. However the FDA believes that these issues transcend a naming convention. It would be the U.S. FDA's preference that INNs continue to be granted based only on molecular characteristics and pharmacological class of the active ingredient(s). Regarding similar protein products, this view is predicated on the situation in the U.S., where there are alternative mechanisms in place for preventing potentially dangerous substitutions and ensuring that potentially unsafe drug dispensing decisions are not made because of a misperception that the same INN implies pharmacologic interchangeability. These mechanisms might not exist in other countries. In the event that granting the same INN name to similar drugs that are nonetheless pharmacologically distinct may lead to inappropriate substitutions, then it may be determined at a later date that changes to the INN policy are needed to ensure safe prescribing and dispensing of drug products including similar protein products throughout the world. Concerns about inappropriate substitutions that can create safety issues may be beyond the scope of the INN program to address through nomenclature alone, and may be better addressed by specific steps taken by individual regulatory authorities to ensure appropriate prescribing."

Pharmacovigilance:

In the USA, the non-proprietary name may serve as a useful tool in pharmacovigilance as it may be one means of product identification, but it should not be relied upon as the sole means of product identification. Pharmacovigilance is the dual responsibility of the manufacturer and the U.S. FDA. In order to practice the most robust pharmacovigilance, all involved should employ all the various tools available for product identification, including lot numbers, NDC codes or other such national coding systems, etc.

As such, the USA does not see any reason to change present INN practices for pharmacovigilance purposes when there are other identification systems in place to allow product identification beyond the level of the non-proprietary name.

U.S. FDA Concerns Regarding INNs and Complex Proteins

If the outcome of assigning the same INN to two products with highly similar ingredient(s) created the implication that the two products were pharmacologically interchangeable AND there were NO scientific data to support that finding, then the U.S. FDA would have serious concerns about such an outcome, especially with more complicated proteins. As of today, FDA has not determined how interchangeability can be established for complex proteins.

If the outcome of assigning different names or names with unique identifiers to two products with highly similar active ingredient(s) created the implication that two

products were not interchangeable when indeed there were scientific data establishing such, the U.S. FDA would have serious concerns.

It is beyond the role of the INN Expert Committee to make product interchangeability determinations. This would place an unrealistic burden of responsibility with accompanying liability on the INN Expert Committee. The INN should not be used as a determinant of interchangeability. It would be bad public health policy to allow, just because they share the same INN, the substitution of products with a shared INN in patient care when there are no scientific data to demonstrate pharmacologic interchangeability.

Likewise, it would be bad public health policy to disallow, solely because they have different INNs, the substitution of products with different INNs which indeed have scientific data that demonstrate pharmacologic interchangeability.

Each national regulatory authority should oversee the evaluation of interchangeability based on bioequivalence and/or other validated scientific data and not link such decisions to INNs.

Conclusions

This discussion among national regulatory authorities and the WHO should be a first discussion on this issue to fact find and to determine how changes to the INN system would impact both positively and adversely, the regulatory systems and public health of WHO member states.

- The FDA is concerned that some countries may be using the INN as an indicator of interchangeability. Although this is not the case in the U.S., the U.S. FDA considers this apparent inappropriate use of the INN to be a public health concern.
- The U.S. FDA encourages the WHO to further investigate the worldwide prevalence of using the INN as a determinant of interchangeability (note: the BCG study sponsored by Amgen investigated 6 EU countries and use of the INN in prescribing was encouraged in most of these 6 countries, but not required).
- The U.S. FDA suggests that the WHO/INN Expert Committee clarify and re-iterate the intent of the INN with participating countries.

It would be the U.S. FDA's preference that INNs continue to be granted based only on molecular characteristics and pharmacological class of the active ingredient(s). Regarding similar protein products, this view is predicated on the situation in the U.S., where there are alternative mechanisms in place for preventing potentially dangerous substitutions and ensuring that potentially unsafe drug dispensing decisions are not made because of a misperception that the same INN implies pharmacologic interchangeability. These mechanisms might not exist in other countries. In the event that granting the same INN name to similar drugs that are nonetheless pharmacologically distinct may lead to inappropriate substitutions, then it may be determined at a later date that changes to the INN policy are needed to ensure safe prescribing and dispensing of drug products including similar protein products throughout the world. Concerns about inappropriate substitutions that can create safety issues may be beyond the scope of the INN program to address through nomenclature

alone, and may be better addressed by specific steps taken by individual regulatory authorities to ensure appropriate prescribing."

At this time, the U.S. FDA acknowledges that biosimilars have not been demonstrated to be interchangeable through any scientific process. The world community may ultimately decide that INN policy for this class of products should be treated differently than that for small molecule drugs. A different naming scheme for these products might involve utilizing a different level of granularity, which may be more detailed or less detailed depending upon the utility in the INN system. Considering the inherent difficulties in additional INN product distinctions (e.g. retroactive and lifecycle changes in naming, additional INN responsibility and liability), if the world community decides to proceed with a change in the policies regarding the assigning of INNs, it should be preceded by (a) appropriate exploration of alternatives (e.g. improvements in education and/or labeling), (b) assuring the such changes fall within the scope, competence, and expertise of the INN program, and (c) the performance and independent validation of a formal risk assessment and/or documentation of events with appropriate statistical treatment.