April 16, 2012

Via Electronic Submission at http://www.regulations.gov

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

RE: Docket Nos. FDA-2011-D-0611 (Q&A); FDA-2011-D-0602 (Quality); FDA-2011-D-0605(Scientific Considerations); FDA-2012-N-0129 (Information Collection)
FDA Draft Guidances For Industry In Connection With The Agency’s Implementation Of The Biologics Price Competition And Innovation Act of 2009

Dear Sir/Madam:

Mylan Inc. (“Mylan”) welcomes this opportunity to comment on the three draft guidance documents that the Food and Drug Administration (“FDA”) issued in connection with the Agency’s implementation of the Biologics Price Competition and Innovation Act of 2009 (“BPCI Act”).

Mylan is the world’s third largest generic and specialty pharmaceutical company and the largest global generics company headquartered in the United States. Today, one out of every 11 prescriptions dispensed in the United States, brand or generic, is a Mylan product. Over the course of its 50 year history, Mylan has demonstrated an unwavering commitment to enhancing patient access to high-quality, affordable generics, which are equally as safe and efficacious as their brand counterparts. As part of that commitment, Mylan is taking a leading role in the development of biogenerics for the U.S. marketplace and currently has six products in various stages of development. Following careful evaluation of FDA’s draft guidances, the accompanying comments are offered to constructively contribute to FDA’s implementation of this critically-important regulatory pathway.

Mylan believes that in order for a biogenerics pathway in the U.S. to successfully expand patient access to lifesaving biologic therapies, consistent with the overall intent of Congress, it must be predicated on the establishment of a substitution-based biogenerics marketplace that utilizes current science. This premise is the foundation of the Hatch-Waxman Act of 1984, which created the U.S. generic drugs market as we know it today, and which has led to more

---

1 The guidance documents are entitled: “Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009”; “Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product”; and “Scientific Considerations in Demonstrating Biosimilarity to a Reference Product”.

than $930 billion of savings in the U.S. over the last decade as a result of the use of generic prescription drugs in place of brand name counterparts.\(^2\)

In that same spirit, Mylan appreciates the significant effort that FDA has put into issuing guidance to implement the biogenerics pathway, and Mylan looks forward to continuing to work with FDA to shape the pathway to ensure that a robust and operable regulatory framework is established to enable U.S. patients to gain access to biogenerics that are equally safe and effective as their brand counterparts. In this regard, Mylan believes that FDA should be commended for several positive aspects of the guidances, which will advance biogeneric development, including: permitting use of a foreign comparator product; allowing for extrapolation of indications; permitting carve-outs of indications; and allowing for approval of fewer than all routes of administration.

Moving forward, as its first order of business, Mylan urges FDA to establish an Office of Biogenerics within the Agency, similar to the Office of Generic Drugs, but tasked with expediting patient access to equally safe and efficacious, interchangeable, and more affordable biogenerics. The creation of a new Office of Biogenerics dedicated to these products will enable the Agency to focus resources, including appropriately dedicating biosimilar user fees and funding levels solely to biogenerics, and a separate office is also the best way to make certain that biogenerics receive a priority high enough to ensure timely review and patient access.

Additionally, Mylan urges FDA to issue more tactical guidance and instruction on filing abbreviated BLAs under the pathway, in order to provide a level of detail similar to that which FDA outlined in the letter dated October 11, 1984, that FDA issued to industry just after Hatch Waxman's enactment in order to provide needed clarity to supplement the pathway described in the underlying statute.\(^3\) Just as FDA issued such a communication to kickoff the generic-drug approval pathway, FDA should undertake the same for the biogenerics pathway as soon as


possible, as nearly two years have now passed since enactment.

Through the BPCI Act, Congress developed an abbreviated-application mechanism for biogenerics, by leveraging current science as well as the wealth of prior knowledge about previously-licensed brand biologics, to enable accelerated biogeneric development and approval, thereby giving U.S. patients access to biogenerics with the same high quality and delivering equivalent safety and efficacy outcomes as their brand counterparts.

Congress expects that biogenerics will introduce price competition that reduces health-care costs while delivering equivalent clinical outcomes. As has been underscored by the Administration and multiple advocates and stakeholders, effective biogeneric competition is a necessity to the sustainability of today’s health care system, given the very high costs of current biologic treatments, which often run in the tens of thousands of dollars for a single patient for a single course of treatment.

To fulfill that intent of enhanced access to affordable biologic treatments, Congress granted FDA authority to classify biogenerics as interchangeable, just as Congress in 1984 granted FDA the comparable authority for generic drugs in Hatch-Waxman. Interchangeability is the cornerstone of such a pathway, and the critical driver to achieving increased access and affordability. Consequently, interchangeability, which is scientifically-attainable, is the only way to truly achieve the anticipated savings available from biogenerics. Many of the same initial debates that we are hearing today are the same ones that FDA and the generic drugs industry heard in 1984, when many questioned the ability of generic drugs to demonstrate interchangeability with their brand counterparts. Fortunately, science prevailed in 1984, and U.S. consumers and the healthcare system owe the unparalleled savings from these generic drugs over the past 28 years to the fact that FDA chose, after Congress’ enactment of Hatch-Waxman, to focus on the science supporting interchangeability rather than the rhetoric against it. This science clearly demonstrated that these FDA-approved generics delivered clinically-equivalent outcomes to patients through AB-rated and fully-substitutable generic drugs.

Sound science and currently-available state-of-the-art analytical tools allow biogeneric sponsors to demonstrate that their biogenerics are “highly similar” to their brand counterparts and will deliver equivalent clinical safety and effectiveness outcomes. Meeting this “highly similar” standard has enabled originator brand biologics to be modified (through process and/or formulation changes) and yet also interchangeable in the marketplace with the earlier, unmodified version of the originator brand biologic. Yet, the draft guidances, as currently written, create an unnecessarily-higher bar for biogenerics than is applied to brand biologics that meet the “highly similar” standard after having undergone process and formulation changes, and thus does not establish a realistic and workable pathway to biogenerics interchangeability.
We also believe that the guidances have the effect of creating an unlevel playing field for biologics regulation between originator biologics and biogenerics. Some of the apparent inconsistencies between the requirements in the guidance and FDA’s longstanding science-based regulation of biologics could impede development and approval of equally safe and effective biogenerics and thereby defeat the purpose of the BPCI Act.

Specifically, and as detailed in our accompanying submission, Mylan is concerned that the draft guidance documents raise the following scientific issues:

A. Not applying over 15 years of consistent regulatory practice with respect to biologics meeting the “highly similar” standard and appropriately collapsing biosimilarity and interchangeability determinations;
B. Increasing regulatory burden for utilizing a foreign comparator product;
C. Imposing a heightened regulatory burden for extrapolation of indications;
D. Requiring pediatric development as a premise of biogeneric development;
E. Caveating the anticipated grant of biogeneric label carve-outs;
F. Requiring evaluation of additional routes of administration (beyond those for which biogeneric approval is sought) for a basic biogeneric approval;
G. Requiring biogenerics to include an unprecedented labeling statement that the product is a biosimilar and that the product has or has not been determined to be interchangeable; and
H. Omitting any indication that a “highly similar” biogeneric shall retain the identical USAN/INN as the brand biologic against which the biogeneric is shown to deliver equivalent clinical outcomes.

If these higher regulatory hurdles, which are inconsistent with how originator biologics are treated, are maintained for biogenerics, these requirements will affect the viability of the abbreviated approval pathway for biogenerics and thereby impact the critical public policy objective of bringing affordable, high-quality biogenerics to market that will deliver equivalent clinical outcomes to American patients and the U.S. healthcare system.

Most specifically, if a biogeneric manufacturer can demonstrate that its product falls within the limits of the variation of the innovator product and that the biogeneric is “highly similar” in all other respects, that demonstration should support the scientific and regulatory conclusion that the biogeneric can be expected to produce the same clinical result in any given patient. Accordingly, FDA should classify a “highly similar” biogeneric as interchangeable.

Mylan is confident in FDA’s ability to exercise its authority appropriately in reviewing and licensing high-quality biogenerics which have the same safety, purity, and potency as their
brand biologic counterparts and that can enable patient access to affordable biologics that deliver equivalent clinical outcomes. FDA’s expertise and experience, as well as the powerful scientific tools presently available to both the biogenerics industry and FDA (many of which were unavailable to the companies that developed most brand biologics on the market today), enable FDA to achieve these critically-important public-health outcomes, which will advance the public health and create robust competition between biologics. Mylan looks forward to assisting FDA in these efforts.

Respectfully submitted,

Dr. Patrick Vink
Senior Vice President
Mylan Inc.

Enclosure
SCIENTIFIC ISSUES ARISING FROM DRAFT BIOSIMILAR GUIDANCES: REQUIREMENTS THAT ESTABLISH AN UNLEVEL PLAYING FIELD FOR BIOGENERICS AND DEFEAT THE PURPOSES OF THE BPCI ACT

SUBMISSION OF MYLAN INC.

A. Consistent With Application Of The Well-Established “Highly-Similar” Standard, FDA Should Combine Its Biosimilarity And Interchangeability Determinations For Any Biogeneric Demonstrated To Be “Highly Similar” To Its Reference Product

The “Highly Similar” Standard Adopted By ICH Under FDA’s Leadership Is The Interchangeability Standard For Biologics And Should Be Applied To Biogenerics

Under the draft guidances, a realistic and workable pathway to biogeneric interchangeability does not currently exist, frustrating the very purposes of the BPCI Act, which sought to open access to expensive biologics by creating the pathway for approval of biogenerics and thereby generate billions of dollars in savings to U.S. consumers, payors, and the government. The guidances overlook the fact that interchangeability of biologics has already been established scientifically, and FDA already has made interchangeability determinations for any number of modified Public Health Service Act biological products as a result of the science-based “highly similar” standard that was adopted internationally through the International Conference on Harmonization (“ICH”) process of Technical Requirements for Registration of Pharmaceuticals for Human Use.

---

4 This is addressed in Q.I.14./A.I.14. of the draft Q&A Guidance and on page 4, lines 142-148, of the draft Quality Considerations Guidance.

5 The draft guidances refer to interchangeability as involving a “higher standard” and underscore that an interchangeable biogeneric both “must be shown to be biosimilar to the reference product and meet the other standards described in section 351(k)(4)”. The guidances also indicate that interchangeability involves a “sequential” assessment in a supplemental aBLA following approval of an original biogeneric aBLA. As a result, the guidances suggest that interchangeable biogenerics are not presently achievable and will not be possible until some unspecified future time point.

Over the years, through the Agency’s implementation and the brand biopharmaceutical industry’s leveraging of the “highly similar” standard in comparability, FDA has approved many biologic manufacturing changes and determined that the modified brand biologic is comparable to the pre-changed brand biologic, thereby enabling both biologics to be on the market and freely interchangeable with one another as supplies of the pre-modified biologic are depleted and supplies of the modified biologic come on-line. As a result, many brand biologics on the market today are “interchangeable biogenerics” of the original biologics FDA approved years and sometimes decades ago. Interchangeability of brand biologics has been facilitated by a significantly different regulatory burden (typically, just analytical testing) than the burden which the draft guidances apply to biogenerics just to get approved without interchangeability.

As a result of FDA having pioneered the “highly similar” standard over 15 years ago (in 1996), the Agency has a wealth of experience with the standard and has defined an interchangeability standard for biologics (even if the Agency is not specifying it by using interchangeability nomenclature). It is this very same standard and outcome which Congress adopted in the BPCI Act for biogenerics. Consequently, FDA and the patients it serves can be confident that the sound, science-based standard which Congress adopted for biogeneric applications is well-understood, has been applied consistently by FDA to modified versions of previously-

---

7 As a matter of statutory construction, it cannot reasonably be debated that, from a legal perspective, the undefined term “highly similar” in the BPCI Act adopts the meaning the term has always had for biologics having the same regulatory consequences for “highly similar” biogenerics as it does for “highly similar” branded biologics. This is because, applying standard canons of statutory construction, when Congress enacts in a statute a highly-technical term of art in a highly-regulated environment and leaves the highly-technical term of art undefined in the statute, Congress is presumed to be adopting the established regulatory meaning of that term of art as it is being applied by the responsible regulatory agency at the time of the statute’s enactment. See, e.g., McDermott Ina, Inc. v. Wilander, 498 U.S. 337, 342 (1991) (“In the absence of a contrary indication, we assume that when a statute uses such a term [of art], Congress intended it to have its established meaning”); United States v. Cuomo, 525 F.2d 1285, 1291 (5th Cir.1976) (courts must “interpret particular words of a statute in their commonly understood sense, unless the statute obviously requires a different interpretation”). See also Sullivan v. Stroop, 496 U.S. 478, 483 (1990) (observing that “where a phrase in a statute appears to have become a term of art . . . any attempt to break down the term into its constituent words is not apt to illuminate its meaning”). By definition, a term must have an established and settled meaning to constitute a term of art. See, e.g., Stewart v. Dutra Constr. Co., 543 U.S. 481, 487 (2005). Moreover, a term of art must have an established and settled meaning in the industry. In re Pharmaceutical Industry Average Wholesale, 460 F.Supp.2d 277 (D. Mass., 2006). “To be sure, there are instances where a statutory or regulatory term is a technical term of art, defined more appropriately by reference to a particular industry usage than by the usual tools of statutory construction.” U.S. v. Lachman, 387 F.3d 42 (1st Cir., 2004) (citations omitted). Consistent with the requirement of this canon of statutory construction that the term actually be a technical term of art, here, there can be no reasonable dispute that the term "highly similar" has a well-established, commonly-accepted technical meaning in the relevant (biopharmaceuticals) industry as well as for the relevant regulatory agency (FDA) that has responsibility for applying it. Accordingly, the courts would conclude that “highly similar” is a technical term of art, and its established technical meaning is the one adopted in the BPCI Act.
licensed biologics since 1996, and continues to enable the same regulatory determinations today for all “highly similar” biologics.

Indeed, it is essentially this same approach that underlies FDA’s ground-breaking approval of an interchangeable “generic biologic” drug just two years ago, when FDA approved an ANDA for a generic enoxaparin—pursuant to the FD&C Act’s 505(j) pathway in which FDA is statutorily precluded from requiring clinical trials. In doing so, FDA appropriately relied upon data generated by presently-available, state-of-the-art analytical tools to conclude that generic enoxaparin is not only similar to but the same as Lovenox, and therefore can be classified as an A-rated, therapeutically-equivalent generic fully-interchangeable with the brand—despite the fact that both the brand and generic biologic drug are structurally diverse and far more complex than most biogenerics that would be approved under the BPCI Act.

---

8 As FDA detailed in its 45-page response to the brand biologic drug manufacturer’s 7-year-old Citizen’s Petition:

> In sum, we can reasonably conclude (provided there is equivalence of physicochemical properties) that if the ANDA applicant for enoxaparin shows that it uses the equivalent heparin source material and equivalent mode of depolymerization as that used for Lovenox's enoxaparin, then the resultant mixture of oligosaccharides will be at least similar with respect to both (1) the distribution of "natural" sequences of disaccharide units in the oligosaccharide chains and (2) diversity of the modified disaccharide building blocks at the terminal ends of the oligosaccharide chains. This provides important information for demonstration of enoxaparin sameness, but it is not sufficient by itself to conclude enoxaparin sameness. Satisfaction of the remaining three criteria in addition to the previous two criteria, however, would be sufficient to demonstrate that the molecular diversity of the generic drug product's enoxaparin and Lovenox's enoxaparin will be equivalent and, therefore, provides sufficient information to conclude that the generic drug product's enoxaparin and Lovenox's enoxaparin are the same.


9 Notably, the entrenched incumbent whose longstanding monopoly was finally thwarted by FDA’s approval of substitutable generic enoxaparin acknowledged FDA’s determination that these extraordinarily-complex biologic drugs had been shown to be highly similar: “FDA has satisfied itself that Lovenox and [the generic] product are highly similar.” Reply in Support of Application of Plaintiff Sanofi-Aventis for Temporary Restraining Order and a Preliminary Injunction, Case 1:10-cv-01255-EGS (DDC, Aug. 11, 2010), at page 18. Despite that concession, it is anticipated that its advocates will argue in the context of FDA’s biogeneric guidances that the “highly similar” standard for biogenerics is different than the “highly similar” standard for brand biologics.
FDA’s Wealth Of Scientific Expertise And Experience Implementing The “Highly Similar” Standard Promulgated By FDA Should Guide Implementation Of The BPCI Act

It is this scientific experience that must guide implementation of the biogenerics pathway. The relevant regulatory and scientific history for applying this approach to biogenerics dates back to the early-1990s, when brand biologics manufacturers were scaling up their processes and were seeking ways to reduce regulatory burden when making substantial changes to their processes to meet market demand. FDA was concerned that process changes could affect product attributes and, as a result, impact safety and efficacy. FDA solved the problem in 1996 through its Comparability Guidance, “Demonstration of Comparability of Human Biological Products, including Therapeutic Biotechnology-derived Products”.  

The “highly similar” standard that FDA established in 1996 to enable comparability assessments extended to all biologic products, regardless of relative complexity, regulated by both CDER and CBER, including both PHS Act biologics as well as FD&C Act biologic drugs. Importantly, FDA exercised its authority to assess and designate pre- and post-manufacturing change biologics as “highly similar” and therefore interchangeable under the PHS Act long before the BPCI Act was ever enacted. Not surprisingly, FDA’s comparability guidance and its “highly similar” standard was supported wholeheartedly by the brand biologics industry, as it reduced development timelines and cut R&D costs significantly based upon a scientifically-valid comparability exercise. As a result, comparability protocols showing modified biologics to be “highly similar” have been used extensively by the majority of brand biologic sponsors.

For more than 15 years following adoption of the “highly similar” standard in 1996, FDA has gained extensive experience in comparing “highly similar” modified biological products when conducting reviews of manufacturing changes, addition of new facilities, changes in cell line, etc. Each time, as is the case under the BPCI Act, the sponsor has borne the burden of collecting the necessary data to support the validity of its comparability approach to demonstrate that its modified and previous biologics are “highly similar”. Importantly, these comparability exercises have rarely entailed clinical trials, and they have never required switching studies between a pre- and post-manufacturing change biologic to show that the new, modified version of the biologic can be switched without intervention by the healthcare provider who prescribed the earlier, unmodified version of the biologic.

There Is No Evidence Of Any Immunogenicity Reactions Involving Two Marketed Biologics That Have Met The “Highly Similar” Standard And Been Interchanged

Throughout this process of “highly similar” determinations and the ensuing interchangeability of “highly similar” brand biologics, it never has been suggested that the use of comparability or the interchangeability in the marketplace of “highly similar” brand biologics has put patients’ safety at risk.\(^\text{11}\) Indeed, switching between “highly similar” pre- and post-manufacturing change brand biologics has not been considered of substantial concern by regulators, industry or consumers. This holds true despite the fact that application of the “highly similar” standard typically has enabled modified brand biologics to be treated as interchangeable in the marketplace on the basis of analytical data alone.\(^\text{12}\)

Importantly, even though the “highly similar” modified and legacy brand biologics have been on the market simultaneously, there has been no reported increase of immunogenicity or safety issues. To the contrary, modified brand biologics that FDA has found to be “highly similar” and that have become interchangeable in the marketplace have continued to deliver the safe and efficacious outcomes as the legacy biologics they replaced – and biogenerics that meet the “highly similar” standard will do the same and should be equally interchangeable without having a higher regulatory burden imposed. For example, it is not consistent with current science or the “highly similar” standard adopted in the BPCI Act to require a biogeneric sponsor to undertake development steps that have not been required for brand biologics seeking to meet the same “highly similar” standard, such as powering a clinical study based on immunogenic response,\(^\text{13}\) which could necessitate enrollment of an extraordinarily-high


\(^\text{12}\) Comparability for a manufacturing change is usually dependent on analytics, without any preclinical or clinical studies at all, with few comparability assessments requiring anything more than analytical data. See 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, available at http://www.fda.gov/NewsEvents/Testimony/ucm154070.htm (comparability “may be demonstrated through different types of analytical and functional testing and might not require additional clinical studies”).

\(^\text{13}\) See Scientific Considerations Draft Guidance, at page 14, lines 535 et seq. Moreover, the provision that biogeneric “[s]ponsors should consult with FDA on the sufficiency of assays before initiating any clinical immunogenicity study,” ibid. at page 16, lines 615-616, is not consistent with industry practice generally or application of the “highly similar” standard in particular and will result in unnecessary delays in development of biogenerics.
number of patients in a study that is not scientifically justified as an across-the-board requirement.

In this context, Mylan is cognizant of the oft-presented contentions advanced by those who contend that interchangeability of biosimilars should only be implemented far in the future (if at all). However, as was the case in 1984, when the same thing was said about small molecule interchangeability before and after Hatch-Waxman, these arguments are baseless. Opinions along these lines typically revolve around the unfounded assertion that interchangeability of biogenerics will increase the risk of immunogenicity reactions in patients. In fact, there is absolutely no evidence that a biosimilar product required to meet the “highly similar” standard and approved by a regulatory authority as a biosimilar pursuant to a biosimilar regulatory framework has ever produced an immunogenicity profile post-approval that differs in any way from that of its brand biologic counterpart. Thus, there is no report to this effect for any approved biosimilar marketed in Europe, Australia, Canada, or other jurisdiction that has approved “highly similar” biogenerics.

**The Guidances Should Apply Current Science Built On Over 15 Years’ Experience With The “Highly Similar” Standard Rather Than The Legacy “Product Is The Process” Approach**

Despite this over decade and a half long history of success in applying the “highly similar” standard, and despite the myriad of advancements in analytical techniques over the course of that history that enable biogeneric sponsors to do at least as good if not a better job analyzing brand biologics than their brand counterparts ever did, the draft guidances do not apply current science in suggesting that the “highly similar” standard from comparability is scientifically inapplicable to biogenerics. Unfortunately, the draft guidances base this suggestion on the “product is the process” rubric that was rendered obsolete over 15 years ago by FDA’s comparability guidance.

“Different manufacturing processes may alter a protein product in a way that could affect the safety or effectiveness of the product. . . .Demonstrating that a proposed product is biosimilar to a reference product typically will be more complex than assessing the comparability of a product before and after manufacturing changes made

---

14 When representatives of brand biologic manufacturers advance such contentions, they do not ever link these arguments to their modified brand biologics that have met the “highly similar” standard or suggest that their “highly similar” products have any risk of immunogenicity reactions being associated with their routine interchangeability. This is the case despite the fact that the only significant experience with biologics’ immunogenicity has been in the context of brand biologics that met the highly similar standard.

15 Those outdated product is the process analyses are on page 5, lines 146-152 and 168-192, of the draft Scientific Considerations Guidance, and page 3, lines 104-117 of the draft Quality Considerations Guidance.
by the same manufacturer. This is because a manufacturer who modifies its own manufacturing process has extensive knowledge and information about the product and the existing process, including established controls and acceptance parameters. In contrast, the manufacturer of a proposed product will likely have a different manufacturing process (e.g., different cell line, raw materials, equipment, processes, process controls, and acceptance criteria) from that of the reference product and no direct knowledge of the manufacturing process for the reference product. Therefore, even though some of the scientific principles described in ICH Q5E may also apply in the demonstration of biosimilarity, in general, more data and information will be needed to establish biosimilarity than would be needed to establish that a manufacturer’s post-manufacturing change product is comparable to the pre-manufacturing change product.\textsuperscript{16}

In fact, use of comparability’s “highly similar” standard along with advances in analytical science have demonstrated and re-confirmed that the product is no longer the process.\textsuperscript{17}

Contemporary technologies now allow thorough characterization, such that a biogeneric sponsor can undertake direct analysis of key features critical to safety and efficacy. Advances in analytical science currently permit in-depth, reproducible chemical structural analyses and enable the direct comparison of the structure and composition of a biogeneric with its brand counterpart. This crucial and continuing progress in the technology vastly reduces dependence on a single proprietary manufacturing process to determine whether two products are highly similar. In fact, the analysis of both the biogeneric and originator products will be performed to a depth and detail substantially beyond that which was ever done for many brand biologics on the market today. Indeed, today’s microanalytical technology can be expected to identify differences in the structures of both naturally-occurring molecules – and in the innovator’s marketed, first generation material – which will reveal the presence of molecular variants that have never before been identified in the originator’s marketed product.

\textsuperscript{16} Draft Scientific Considerations Guidance at page 5, lines 146-152 and 168-192.
\textsuperscript{17} A product that not only paved the pathway for biogenerics, but in many respects effectively constituted the first biogeneric itself, is Avonex\textsuperscript{®} (interferon beta 1a). As has been well documented in court filings and public policy debates, Biogen “broke the mold” by eliminating the age-old paradigm of “the product is the process,” thereby forever changing the biologics world. In doing so, Biogen validated the scientific and regulatory science principle of comparability that is the basis for all biologics today, including biogenerics. Based on its limited BLA filing, FDA determined that Biogen had demonstrated comparability of two biogeneric products from a different cell-line, a different manufacturing facility with a different manufacturing process based solely on analytics – without a single comparative clinical trial, let alone a head-to-head clinical trial – all the very same “differences” that many opponents of biogenerics still point to today as purported rationales for increased regulatory burden for true biogenerics.
This major progress in analytical science has been paralleled by improved instrumentation, increased automation of new and existing technologies, improved sensitivity through miniaturization (and the associated need for smaller samples), with the net result of enhanced accuracy and reproducibility of results. In addition, advances in methods development have improved analytical strategies and test protocols, notably by use of recently developed computer hardware and software. Together, these powerful, currently-available, state-of-the-art analytical tools combine to give enhanced selectivity and separation power which allow an even more detailed demonstration that a biogeneric is “highly similar” to its brand counterpart than the brand is to itself. It is for these reasons that it does not matter if the processes by which a given biologic was produced remain confidential and exclusive to the originator manufacturer, because new technologies enable a biogeneric to be developed and compared to that earlier product, with the presence of any clinically-meaningful differences being identified.

Accordingly, the same “highly similar” standard that has been applied for over 15 years to originator biologics, having now been adopted for biogenerics in the BPCI Act, must be applied equally when assessing a biogeneric product in comparison to its reference product. Indeed, in Europe, the comparability concept was considered of great value for all stakeholders, and the European use of the term comparable extended to products from different sponsors right from the start.\(^\text{18}\) Comparability then became the basis for biosimilars being approved in Europe, and these EMA efforts pioneered approval of “highly similar” biogenerics that expressly reference the prior approval of a product from a different sponsor.\(^\text{19}\)

As a result of FDA’s leadership and extensive work in implementing its 1996 comparability guidance and the ICH Q5E guideline, FDA already has accumulated a wealth of experience applying the “highly similar” standard to biologics having a diverse range of complexities, including fused proteins and monoclonal antibodies. FDA must draw on the same science of comparability for biogenerics as has been applied to first-generation brand biologics. This will put FDA’s biogeneric approval program on firm scientific footing, as well as ensure its adherence to the law, and enable approval of biogenerics that are just as safe and efficacious as their brand biologic counterparts.

---


Sound Science And Consistent Regulatory Policy Should Lead FDA To Apply The Same “Highly Similar” Standard – In The Same Manner And With The Same Effect – To All Biologics From All Sponsors Demonstrating That Biologics Produced From Distinct Manufacturing Processes Are Nonetheless “Highly Similar”

Yet, the draft guidances do not apply the same “highly similar” standard and comparability approach or reach the same outcome for biogenerics as FDA has reached countless times for brand biologics. As a result, the draft guidances effectively assume that what is not measured during a manufacturing change for a brand biologic is unaltered, but what is not measured for a biogeneric is dissimilar until it is affirmatively shown not to be different. It is scientifically inappropriate for the guidances to apply a different standard than that which applies to modified brand biologics for evaluating interchangeability of biogenerics that are shown to be at least as “highly similar” to the brand as the brand is to itself. Moreover, this approach in the draft guidance documents undermines physician and patient confidence in FDA’s evaluation as to whether any biologics – brand biologics and their biogeneric counterparts – are truly “highly similar”.

Mylan agrees with FDA that it is critical that biogeneric applications demonstrate similarity at the nonclinical analytical level, based on a standard of “highly similar” quality attributes using a comparability exercise conducted with existing state-of-the-art analytical methodologies, applying an orthogonal approach such as is readily available today. It is with the demonstration that a biogeneric is “highly similar” at the biochemical/biophysical level that the waiver, or abbreviation, of preclinical and/or clinical studies is warranted. Accordingly, as indicated in the draft guidance documents, any analytical differences between the biogeneric and its reference product must be explained and justified in terms of efficacy and safety of the biogeneric product. However, this does not mean that interchangeability should be a proverbial “dead letter” in the law or that interchangeability status should improperly be denied to “highly similar” biogenerics.

Moreover, biogenerics should not require a different standard to achieve interchangeability, as this inappropriately and unscientifically suggests that “highly similar” biogenerics are somehow of a lower quality than their brand biologics counterparts are in a brand-to-brand comparability assessment. All biologics, including the brand biologic reference product and biogenerics, must be of equal quality, safety, purity, and potency, and they should all be judged by the same standards, which should result in the same regulatory outcomes. Accordingly, there is no need for an extra step and a separate approval. Instead, based upon the draft guidance provided, a biogeneric should be classified as interchangeable once the biogeneric meets the “highly similar” standard in the manner in which FDA has prescribed.
Just like a brand biologic that meets the “highly similar” standard is effectively classified as interchangeable, so too should a biogeneric be classified as interchangeable once it has met the “highly similar” standard. Indeed, for the guidances to require any further evaluation of and data on a biogeneric is not scientifically justified, would result in unnecessary, duplicative, and sometimes unethical testing, and it would not provide any further meaningful scientific support for an interchangeability classification beyond what already has been established by demonstrating that the biogeneric is “highly similar” and will produce equivalent clinical safety and efficacy outcomes as its brand biologic counterpart. Indeed, additional testing and additional regulatory burden for biogenerics beyond meeting the “highly similar” standard should not be required as a scientific or clinical matter given that patient responses to a biogeneric are vastly more predictable. Therefore, biogeneric sponsors using existing state-of-the-art analytical and validation tools to characterize and confirm that a biogeneric is “highly similar” to the reference product should only be subjected to the clinical or other study requirements to support interchangeability to the extent that such additional regulatory burdens are imposed on an originator biologic in connection with a manufacturing change. The draft guidance documents already have delineated everything that ever needs to be known – by a biogenerics manufacturer or by a regulatory authority – to enable the interchangeable use of “highly similar” biogenerics that will enable patients to achieve equivalent clinical outcomes more affordably.

Finally, the draft guidance documents should not propose to implement a biogenerics pathway that promotes incentives for biosimilar differentiation rather than incentives for biogeneric substitution. This is a perhaps-subtle, but critically-important distinction, but, by promoting interchangeability of biogenerics that have been demonstrated to be “highly similar,” FDA can enable market dynamics that encourage price-based competition among biologics that are equally safe and efficacious, thereby increasing patient access and affordability to high-quality biogenerics and improving savings to the U.S. healthcare system.

In Conclusion, The Science Does Not Support Discrimination In Interchangeability Among Any “Highly Similar” Biological Products

In short, there is no sound scientific basis for discriminating between the interchangeability status of any “highly similar” biologics. Likewise, no basis exists for treating biogenerics differently by having one standard for biosimilarity and a different, higher standard for interchangeability. By adopting this double-standard, FDA elevates the approval standard for interchangeability for biogenerics to a level that, even if achievable (which, notably, even the guidance documents say is not possible under the Agency’s current undefined standard), is not based in sound science and will only serve to unnecessarily drive up biogeneric costs and
impede patient access to high-quality biogenerics with equivalent safety and effectiveness profiles as their brand counterparts, contrary to the intent of the BPCI Act.

Accordingly, consistent with their decade and a half history of comparability outlined above, FDA should treat “highly similar” biogenerics as automatically interchangeable in the same way and to the same extent that FDA treats brand biologics pre- and post-manufacturing changes as automatically interchangeable. When needed, scientifically-sound clinical programs can be pursued to further confirm comparative clinical safety and efficacy. However, Mylan agrees with FDA’s longstanding position that such clinical programs should be mindful of unnecessary duplication of studies in humans which, as the Agency has noted, may present economic and ethical implications. This is the premise of the “highly similar” standard in the comparability context, and it must remain so for biogenerics. Therefore, Mylan respectfully requests that FDA eliminate any suggestion from its draft guidances that interchangeability is an unknown that will require meeting a different standard. FDA should appropriately combine its biosimilarity and interchangeability determinations for “highly similar” biogenerics just as it does for “highly similar” brand biologics.

B. Consistent With Biologic Global Development Programs, Use Of A Foreign Comparator In A Biogeneric Development Program Should Not Trigger A Considerably Different Regulatory Burden, Nor Should Use Of A Foreign Reference Product Be Effectively Precluded For An Interchangeable Biogeneric

Mylan agrees with FDA’s decision in its draft guidances to permit the use of a non-U.S.-sourced comparator product in biogeneric development programs. Enabling the use of global comparators for biogenerics is a scientifically sound judgment consistent with established regulatory practice and the industry’s longstanding practice of global development.

Treating brand biologics and biogenerics equivalently when it comes to the use of foreign comparators in development will maximize the availability of high-quality, equally-safe and – effective, and affordable biogenerics for patients in the U.S., while minimizing scientifically-unnecessary and duplicative studies across jurisdictions. Indeed, across-the-board acceptance of non-U.S.-licensed comparators that are marketed in another highly-regulated market and

---

20 “The agency has a longstanding policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources…and avoiding ethical concerns associated with unnecessary duplication of…human testing”. Rachael E. Behrman, M.D., M.P.H. Associate Commissioner for Clinical Programs Director, Office of Critical Path Programs, FDA, *Follow-on Biologics: A Brief Overview*, NATURE DRUG DISCOVERY (November 2008), Page 12.

21 This is addressed in Q.I.8./A.I.8. of the draft Q&A Guidance, on page 6, lines 204-215, of the draft Scientific Considerations Guidance, and page 9, lines 344-356 of the draft Quality Considerations Guidance.
shown through appropriate data and/or information to be identical or “highly similar” to the U.S. reference product will enhance the feasibility of bringing biogeneric products to the U.S. market – just as it has facilitated brand biologic market entry. However, Mylan does not agree with the extent to which the guidances increase the regulatory burden for using a foreign comparator in a biogenerics program – a significantly different regulatory burden that is not required for biogenerics’ brand biologic counterparts when they undertake global development programs.

First, the draft guidances increase regulatory requirements on the biogeneric sponsor to justify use of the foreign comparator, including requiring the biogeneric manufacturer to provide details on the license holder and manufacturing sites for the U.S. and foreign products, the regulatory status of the foreign product, and the relevance of the foreign clinical development design to a biogeneric approval in the U.S. Second, the guidance documents place an even heavier burden on the biogeneric sponsor to build a bridge between the U.S. reference and foreign comparator, including comparative analytical testing, bioassays/functional assays, and comparative clinical and/or non-clinical PK and/or PD studies. Third, the draft guidances amplify the regulatory burden for a biogeneric approval where a foreign comparator is used by mandating that, irrespective of the foregoing data, the biogeneric sponsor nonetheless still must conduct its analytical program using the U.S. reference product and conduct clinical studies against the U.S. reference product, including at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamic (PD) study. Finally, FDA effectively precludes use of a foreign reference to support an interchangeability determination stating that “clinical comparisons with a non-U.S.-licensed product would be [unlikely to provide] an adequate basis” for interchangeability.

In addition to not applying sound science on these points, Mylan respectfully submits that the draft guidances also are not consistent with the law. The BPCI Act is clear in defining “reference product”. Congress said that reference product “means the single biological product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k)” (emphasis added). According to the BPCI Act, the evaluation against the U.S. reference need only occur “in an application,” i.e., in the data assessment presented by a biogeneric applicant in its 351(k) application. There is nothing in the law that requires any testing against the U.S. reference product. To the contrary, in specifying analytical, non-clinical, and potential clinical testing of biogenerics, Congress conspicuously omitted any reference to U.S. testing or to conducting tests against a U.S. reference product. There is no sound scientific or public policy basis for the draft guidances to go beyond the statute Congress has enacted.

Accordingly, FDA should follow current science as well as the language of the BPCI Act and eliminate any mandatory U.S. testing and any mandatory testing against a U.S. reference
product. Instead, Mylan encourages FDA to develop a sound scientific framework, consistent with the one applied to biologics since the beginning of the biotech revolution, that follows genuine science to determine the appropriate types and level of data or other information that are needed to evaluate comparative data when a biogeneric sponsor utilizes a foreign comparator product in its development program. Taking this approach also will ensure a level playing field among all biologics sponsors and afford an equal opportunity to all biologics manufacturers to pursue global development.

C. Although The Guidances Allow For “The Potential” Of Extrapolation Of Indications, Extrapolation Should Not Be Predicated On Meeting A Heightened Regulatory Burden

Mylan commends FDA for allowing for extrapolation of indications in its guidance documents. However, Mylan is concerned by the manner in which the draft guidances seem to qualify extrapolation, starting from the premise that merely “the potential exists” for extrapolation to be realized by a biogeneric sponsor.

Mylan is particularly concerned by the provisions in the draft guidance providing that, in order to realize that potential, a biogeneric sponsor must submit data from a clinical study sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, along with scientific justification for extrapolation, including data across the indications for the biogeneric and reference addressing, _inter alia_, their (mechanism of action (“MoA”), PK and bio‐distribution, differences in expected toxicities, and any other factor that may affect the biogeneric’s safety or efficacy in each indication. While in certain limited circumstances (e.g., very distinct populations treated by the same biologic but based upon very distinct MoAs) it might be reasonable and appropriate to require such additional data that should be the exception rather than the norm.

This is because the BPCI Act gives a biogeneric applicant full extrapolation without statutorily requiring anything additional and without authorizing the imposition of additional requirements to secure extrapolation. The law provides that a biogeneric can be approved for one “condition” or for all “conditions” of use of the biogeneric’s brand counterpart. The BPCI Act leaves this election up to the biogeneric applicant without giving FDA authority to differentiate between the two and impose higher regulatory burden on a biogeneric applicant whose product is approved for one “condition” than is imposed on a biogeneric applicant whose product is approved for all “conditions” based upon extrapolation. Instead, the law expressly provides that a demonstration that a biogeneric is “highly similar” (in one population

---

22 This is addressed in Q.I.11./A.I.11. of the draft Q&A Guidance and on pages 19-20, lines 758-795, of the draft Scientific Considerations Guidance.
if a clinical study(s) is required) enables the biogeneric applicant to secure approval for all approved indications of use of the reference product if that is the label for which the applicant submits its 351(k) applicant.

For the draft guidances to require repetitive studies across multiple indications is inappropriate. The BPCI Act does not impose such a requirement, and requiring unnecessary and/or unethical repeat studies across populations impedes development of equally safe and effective biogenerics and undermines the important public policy objectives of the BPCI Act. Accordingly, Mylan urges FDA to amend its guidance documents to fully enable extrapolation of indications consistent with the statute.

D. The Guidances Should Not Require Pediatric Development As A Routine Element Of Biogeneric Development

For any non-interchangeable biogeneric – which, for the reasons detailed in section A of this submission, Mylan does not believe exist scientifically or under the BPCI Act – the guidances anticipate that the Agency routinely will require pediatric development as part of the biogeneric development program. In order to effectuate this outcome, the guidances “encourage[]” all biogeneric applicants to submit plans for pediatric studies at the IND stage.

As outlined above, a biogeneric meeting the “highly similar” standard delineated in the draft guidances should be deemed automatically interchangeable. The BPCI Act expressly provides that no pediatric development is required for interchangeable biogenerics. Therefore, a biogeneric product that has met the “highly similar” standard – just like modified brand biologics which are interchangeable once they are shown to be “highly similar” – should not require pediatric development.

Even if this statutorily-compelled conclusion is not accepted, current science and appropriate clinical judgment should prevail when pediatric development plans for “highly similar” biologics are considered. Once the sponsor of any biologic – whether it is an originator’s biologic or a biogeneric – has demonstrated that its biological product is “highly similar” to a reference biologic, it is scientifically and often ethically inappropriate to mandate pediatric testing.

A “highly similar” biologic will deliver clinical safety and effectiveness outcomes to patients that are equivalent to the clinical outcomes delivered by the reference biologic to which it has been shown to be highly similar. Pediatric testing of such a biological product simply cannot be scientifically justified because, in all such cases, it would result in unnecessary duplication of

23 This is addressed in Q.I.15./A.I.15. of the draft Q&A Guidance.
repetitive studies. Moreover, because the equivalent pediatric clinical conclusions apply to the “highly similar” biologic (biogeneric and brand) as apply to the reference to which it is highly similar, no additional clinically-relevant findings beyond those which already are known could be drawn from any additional pediatric testing. Accordingly, Mylan strongly encourages FDA to amend its draft guidances to eliminate specific pediatric-testing requirements for any biogeneric that is shown to be “highly similar.”

E. Although The Guidances Have Permitted Biogeneric Carve-Outs Of Indications, The Anticipated Grant Of Those Carve-Outs Should Not Be Caveated

Mylan commends FDA for allowing a biogeneric to be approved for a subset of the approved indications for which the reference product is approved. This sensible regulatory approach is supported both by sound science as well as the law. However, Mylan is concerned by the way in which this approach was qualified in the draft guidances, which indicates that such label carve-outs “generally may [be] obtain[ed]”.

According to the BPCI Act, a biogeneric applicant can carve out indications in the originator’s labeling. As detailed in section C above, the law clearly provides that a biogeneric can be approved for one “condition” or for all “conditions” of use of the brand counterpart. The law leaves this election up to the biogeneric applicant. Accordingly, Mylan encourages FDA to eliminate any qualifying language on carve-outs and to reflect in its guidance documents that a biogeneric applicant can carve out indications from the biogeneric’s proposed label if the applicant elects to seek approval for less than all of the brand biologic’s approved uses.

24 “The agency has a longstanding policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources...and avoiding ethical concerns associated with unnecessary duplication of...human testing”. Rachael E. Behrman, M.D., M.P.H. Associate Commissioner for Clinical Programs Director, Office of Critical Path Programs, FDA, Follow-on Biologics: A Brief Overview, NATURE DRUG DISCOVERY (November 2008), Page 12.

25 This is addressed in Q.I.7./A.I.7. of the draft Q&A Guidance.

26 It cannot be reasonably disputed that the brand biologic’s FDA-approved label for the reference product is the basis for a biogeneric’s labeling. Under the BPCI Act, as under Hatch-Waxman, a biogeneric sponsor starts with the reference product labeling as the foundation for the biogeneric labeling and incorporates permissible biogeneric-specific revisions, such as trademark, manufacturer name, inactive ingredients, and any carved-out indication(s). In all other respects, the BPCI Act requires biogeneric labeling to be the same as that of the reference product. Accordingly, contentions that biogenerics somehow require unique labeling must not be adopted in the Agency’s guidances.
F. Although The Draft Guidances Appropriately Anticipate Biogeneric Approval For Fewer Than All Routes of Administration, It Is Scientifically And Legally Inappropriate For The Guidances To Require Additional (Off-Label) Routes Of Administration To Be Studied Even For A Standard Biogeneric Approval

Mylan commends FDA for issuing draft guidances that allow for a biogeneric to be approved for fewer than all routes of administration of the reference. However, Mylan is concerned by the guidances’ regulatory approach to biogenerics’ routes of administration, because the Agency has limited the impact of such targeted development by indicating that the regulatory burden for approval of less than all routes of administration “may include” studies involving an off-label route of administration for which biogeneric approval is not requested. For example, FDA notes that even where approval of a particular route of administration is not sought for a biogeneric, it nonetheless may be necessary for a biogeneric applicant to study another route of administration if it might have sensitivity in comparing immunogenicity profiles.

There is no scientific basis or public-policy rationale for the requirement in the draft guidances of conducting any additional study(s) in off-label routes of administration. A “highly similar” biogeneric will deliver the equivalent clinical outcomes in the route(s) of administration in which the biogeneric and its brand counterpart are both approved, and the “highly-similar” biogeneric also can be expected to have the equivalent immunogenicity profile if it were to be used in the off-label route(s) of administration for which biogeneric approval is not being sought.

Moreover, there is no basis in the BPCI Act for requiring any such additional study(s). An approved biogeneric will be labeled for use with the route(s) of administration for which the biogeneric is approved. Requiring that such an approval include broader evaluation of a biogeneric based upon some perceived potential for off-label use in some other route(s) of administration is not within FDA’s discretion or the statutory authority granted in the BPCI Act.

Accordingly, Mylan respectfully requests that FDA eliminate from its draft guidance documents any requirement for any additional study(s) in any route(s) of administration for which a biogeneric applicant is not seeking approval.

27 This is addressed in Q.I.5./A.I.5. of the draft Q&A Guidance.
G. The Unprecedented Requirement That Biogeneric Labeling Must Include A Statement That The Product Has Been Approved As A Biosimilar And That The Product Has Or Has Not Been Determined To Be Interchangeable Is Not Grounded In Sound Public Policy And It Is Not Statutorily Authorized

The draft guidances impose an unprecedented requirement on biogenerics by requiring that the labeling of a proposed biogeneric should include a clear statement advising that “This product is approved as biosimilar to a reference product for stated indication(s) and route of administration(s)” and that “This product (has or has not) been determined to be interchangeable with the reference product”.

As a matter of sound regulatory science and public policy, it is inappropriate for the guidances to require that such statements be added to the label for each approved biogeneric. Indeed, as already has been seen in Europe, such statements will only serve to promote anti-competitive counter-detailing campaigns against biogenerics. One of the more infamous innovator advertisements used in Europe is rather egregiously captioned (according to the translation from German to English), “Similar, but nevertheless different” and goes on to list a series of asserted “Differences”. While those unfounded assertions do not deserve the credence of being reiterated in this submission, it is important to underscore that deriding biogenerics by referring to them simply being “similar, but nevertheless different,” undermines the whole notion of biogenerics as well as generic drugs. It also is contrary to sound science and runs counter to the decade-and-a-half long experience with application of the “highly similar” standard to biologics. Biogenerics are no more “similar but different” from their brand counterparts than their brand counterparts are “similar but different” to themselves. Accordingly, biogenerics do not warrant unique label statements that seem to classify them as such.

The BPCI Act also does not grant authority for supplementation of biogeneric labeling with statements such as those proposed in the draft guidances. To the contrary, the statute requires that biogeneric labeling must be the same as that of the reference product except for statutorily-permissible differences (relating to manufacturer-specific information involving inactive ingredients and conditions of use). See 42 U.S.C. §§ 262(i)(2)(A), 262(k)(2)(A)(iii)-(iv).

---

28 This is addressed on page 21, lines 821-825, of the draft Scientific Considerations Guidance.
29 This includes fear-mongering tactics advanced by some who catalogue a veritable “parade of horribles” that could befall patients if FDA applies sound science and the Agency’s wealth of experience in classifying “highly similar” biogenerics that deliver equivalent safety and efficacy outcomes as interchangeable with their brand counterparts as the law dictates.
30 Thomas Moore, Hospira, Presentation at Sanford Bernstein Biosimilars Conference (December 3, 2009).
Accordingly, in order to forestall the onslaught of abusive claims in the U.S. comparable to those already seen in Europe, Mylan respectfully requests that FDA eliminate the provisions for the proposed labeling statements from its draft guidance documents.

H. Highly Similar Biogenerics That Deliver Equivalent Clinical Outcomes As Their Brand Biologic Counterparts Must Retain The Same USAN/INN As Their Brand Counterparts In Order To Prevent Confusion Among Prescribing Physicians, Health Care Professionals Dispensing And Administering Biologics, And Patients Receiving Treatment

Over the course of the implementation of the biogeneric provisions of the BPCI Act, Mylan has attentively monitored suggestions in multiple public presentations that the Agency believes it needs to establish policy related to unique naming for biogenerics. Mylan continues to hear indications that consideration is still being given to an unprecedented legal/regulatory and policy shift requiring biogenerics to carry different generic names (USANs/INNs/established names) than their brand counterparts to which they have been shown to be “highly similar.” Consequently, Mylan was deeply concerned by the absence of any regulatory approach or policy pronouncement on this critically-important issue in the draft guidance documents.

Any initiative directed at implementing any alternative naming scheme for biogenerics is unwarranted from a policy and public health perspective. Importantly, FDA itself has recognized the importance of treating biogenerics just like any other biologic for naming purposes. In 2006, FDA presented to the World Health Organization (“WHO”), which has responsibility for global naming of biologics and drugs, a well-considered position that the 50-year-old international naming system for biologics and drugs should continue being applied to biogenerics as it always has been to biologics.\(^\text{31}\) Neither the BPCI Act nor any other scientific or policy development supports or warrants a departure from FDA’s original, well-considered position on biogeneric naming.

Moreover, any suggestion that a unique generic name for biogenerics is necessary for pharmacovigilance purposes is misplaced. Good pharmacovigilance depends upon good data collection for every product dispensed, including biologics, most of which are dispensed in the most pharmacovigilance-sensitive setting (hospitals). Distinctive naming for biogenerics simply will not contribute to this effort. Pharmacovigilance of all biological products – including biogenerics – is not done using product names; rather, providers use well-known, standardized data points, including NDCs (“national drug codes”), batch numbers, and lot numbers. Various

stakeholders underscored this point during FDA’s November 3, 2010, public meeting on biogenerics as reflected, for example, by the testimony of pharmacy benefits manager Medco that “there is no viable reason to require unique non-proprietary names in a way that is different from small molecule products.” Notably, FDA’s own Sentinel System – during its “Mini-Sentinel” pilot phase – has shown that FDA itself is effectively addressing traceability concerns by using NDCs.

By utilizing NDCs and other existing regulatory requirements that already are in place and that function effectively without undermining either the U.S. or global generic naming systems or biogenerics in particular, FDA can continue implementing existing approaches to post-market surveillance for all biologics, including biogenerics, and facilitate pharmacovigilance that serves the Agency’s needs as well as the needs of the patients and providers whom FDA and the industry serve. This can be seen today, with generic and brand chemical drugs that share the same generic names and with multi-source branded biologics that share the same generic names: NDC codes work extremely well in facilitating pharmacovigilance for all these identically-named products, and appropriately allowing biogenerics to share the same names as their brand counterparts to which they have been shown to be “highly similar” will not change those results.

There are, however, proactive track-and-trace solutions that can and should be implemented. Toward that end, Mylan is an active member of the Pharmaceutical Distribution Security Alliance (PDSA) and fully supports that coalition’s proposal on end-to-end track-and-trace rules, pedigree and serialization. In addition, Mylan believes there should be a national standard, and Mylan stands ready to collaborate with FDA on implementing such an approach as well as on development of additional means of traceability if the Agency believes that NDCs are not always adequate.

Furthermore, it is apparent that requiring different generic names for “highly similar” biogenerics will not avoid confusion. To the contrary, it actually would spawn confusion among patients, prescribers, and pharmacists. In addition, being a biogeneric and carrying a different name than the brand counterpart would negatively affect biogeneric acceptance, and erect a barrier to the cost savings biogenerics can enable while delivering equally safe and efficacious clinical outcomes.

Finally, unique names for biogenerics would not comport with the law that Congress enacted. The BPCI Act does not grant authority to FDA to assign distinctive generic names to biogenerics.

Accordingly, for all these reasons, Mylan encourages FDA in finalizing its guidance documents to expressly reconfirm the sound views the Agency originally presented to its global peers in 2006 upholding the scientific, policy, and regulatory appropriateness of biogenerics sharing the same generic name as their brand counterparts.

I. The Rationale For Permissible Differences In Delivery Device Or Container Closures Should Be Specified More Clearly In FDA’s Final Guidances

The draft guidances provide that a biogeneric can be approved in an auto-injector device even if the reference product is licensed in a vial presentation so long as the biogeneric meets the biosimilarity standard and “adequate performance data” is submitted, including demonstrating compatibility “through appropriate studies, including, for example, extractable/leachable studies and stability studies” and potentially “performance testing and a human factors study”. In contrast, however, for interchangeable biogenerics – which, as detailed in section A, above, Mylan believes are the only biogenerics contemplated by the BPCI Act – the guidances establish an effective presumption against such differences by requiring evaluation of significant alterations in “critical design attributes, product performance, or operating principles,” or other features “requiring additional instruction to healthcare providers or patients” to enable safe switching between the reference “and one or more interchangeable products”.

Mylan does not presently have specific comments on this approach, other than to note that the scientific bases and rationale for the Agency’s regulatory presumptions are unclear. Accordingly, Mylan respectfully would suggest that FDA should delineate further and specify more clearly the grounds for these approaches to delivery devices and container closure systems for biogenerics to allow for further comment.

J. The Rationale For Requiring Biogeneric Sponsors to Show The Same Content And Concentration For Purposes of Demonstrating the Same Strength Should Be Detailed With Greater Elaboration In FDA’s Draft Guidances

The draft guidances indicate biogenerics must have the same total content of drug substance (in mass/units of activity per container), and the same concentration of drug substance (in mass/units of activity per unit volume), as the reference product including when constituted/reconstituted, with both expressed using the same measure as the reference.

33 This is addressed in Q.I.4./A.I.4. of the draft Q&A Guidance and on page 5, lines 147-150, of the draft Scientific Considerations Guidance.

34 This is addressed in Q.I.12./A.I.12. of the draft Q&A Guidance.
Mylan presently does not have specific comments on this approach, other than to note, as in the preceding section, that the scientific bases and rationale for the Agency’s regulatory presumptions are unclear. Therefore, Mylan respectfully would suggest that, in its final guidance, FDA should delineate further and specify more clearly the grounds for these approaches to evaluating the strength of biogenerics in terms of their content and concentration of drug substance.

K. FDA Can Have Confidence In The Appropriate Exercise Of The Agency’s Discretion Under The BPCI Act In A Manner Consistent With Its Intent

Although there is only one reference to “discretion” in the Q&A Guidance, in a discussion on exercising discretion on waiving studies. In the context of the explicit authority that FDA has been granted on waiver of the statutorily-specified studies – which are the first explicit studies expressly mandated under the PHS Act – Mylan believes that FDA can have confidence in exercising this waiver authority when justified, consistent with application of the criteria for biogeneric approval on an individual-product, individual-application, case-by-case basis. As detailed in the first section of this submission, the Agency’s wealth of experience implementing the “highly similar” standard enables the Agency to do so. Accordingly, the presumption established in the draft guidance documents against exercise of that waiver authority should be excluded when the guidances are finalized.

CONCLUSION

With adoption of the revisions to the draft guidances that Mylan respectfully proposes in this submission, FDA would put in place a sound, science-based, and data-driven biogenerics pathway that will ensure that only high-quality biogenerics are approved and only after they have met the same “highly similar” standard that every other biologics manufacturer must meet, and therefore allow the full savings and access Congress intended patients, payors, and the government to receive when enacting the BPCI Act. Implementation of that pathway moving forward should occur through a dedicated Office of Biogenerics with focused resources that is charged with ensuring timely review and expediting patient access to equally safe and efficacious, interchangeable, and more affordable biogenerics. That new Office of Biogenerics, and the biogenerics industry, should be supported by more tactical guidance and instruction on filing abbreviated BLAs so that industry has a similar level of detail to that which FDA expeditiously provided within a month of Hatch-Waxman’s enactment in 1984 in order to provide needed clarity to supplement the pathway described in the underlying statute. Collectively, the steps Mylan has outlined here will enable the healthcare community and patients to have confidence that affordable biogenerics will deliver the same safety and efficacy profile and equivalent clinical outcomes as their brand counterparts.
Mylan looks forward to working with FDA to implement these revisions, which are focused on the implementation of a meaningful pathway, enabled by currently-available, state-of-the-art science, and facilitated by dedicated resources ensuring timely review of these critical applications, which are essential to enhancing patient access to more affordable biological therapies that deliver equivalent clinical safety and efficacy outcomes as their brand counterparts.