



February 28, 2014

Chairwoman Edith Ramirez
The Federal Trade Commission
Room H-113 (Annex X)
600 Pennsylvania Avenue, NW
Washington, DC 20580

Comments of the Generic Pharmaceutical Association concerning the FTC Public Workshop regarding Follow-On Biologics: Impact of Recent Legislative and Regulatory Naming Proposals on Competition, Project No. P131208.

GPhA represents the manufacturers and distributors of finished generic pharmaceutical products, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic pharmaceutical industry. Our members manufacture more than 90% of all generic pharmaceuticals dispensed in the U.S., and their products are used in more than one billion prescriptions every year. Generics represent greater than 84 percent of all prescriptions dispensed in the U.S., but only 27 percent of expenditures on prescription drugs. Members of GPhA have produced safe and effective biosimilars for sale outside the U.S. for years. GPhA is the sole association representing America's generic pharmaceutical sector in the U.S., while this response letter represents the views of the association these comments may not reflect all member company positions.

Biosimilars and interchangeable biological products hold great promise for consumers and the pharmaceutical industry. By 2016 it is predicted that eight of the top ten drugs on the market will be biologics.¹ This is important because the average daily cost of a brand name biologic product is approximately 22 times greater than a traditional drug.² When biosimilars and interchangeable biological products are approved – patient access and affordability of these critical treatments will increase.

Biologics are medicines that are derived from living cells, and treat many serious conditions. Biosimilars are biologic therapies that can be produced and sold for a lower price than the biologic Reference Protein Product (RPP). Biosimilar development provides a new opportunity to improve access to health care for many Americans to those products with which the FDA is already the most familiar. In 2010, Congress passed the Affordable Care Act, which included a pathway for bringing biosimilar medicines to the American marketplace. Those provisions of the law are known as the Biologics Price Competition and Innovation Act (BPCIA).

A major goal of the BPCIA is to create competition in the marketplace for biologics, thereby expanding access to, and increasing the affordability of, these critical medicines. As its title

¹ Statement of John D. Ludwig, Pfizer. <http://www.future-science.com/doi/pdf/10.4155/tde.11.58>

² Hilary Krame, Why Biologics Remain Expensive, *Forbes* (2009). <http://www.forbes.com/2009/12/03/kramer-health-care-intelligent-investing-pharmaceuticals.html>

suggests, the BPCIA also is intended to stimulate innovation and investment in the next generation of originator biologics and it is mutually beneficial if this happens alongside the availability of biosimilars. The decisions that FDA makes about how to name these therapies will affect patient access, market competition, and global standards.

Consistent International Naming of Biologic and Biosimilar Products

GPhA recommends that all biologics approved under the Section 351(k) pathway are “highly similar;” and intrinsic to their approval by FDA is the expectation that they will have no clinically meaningful differences from the RPP. Therefore they should share the same United States Adopted Names (USAN) name as the RPP.³ This is the same “highly similar” standard as comparable brand products produced by a change in a manufacturing process or facility, which share the same USAN as the original RPP.⁴ The brand retains the same USAN even though it is “comparable” and not identical to the original version of the product when there is a change to the process, cell line or manufacturing facility from that which was originally approved.

Conversely, GPhA believes that adoption of unique non-proprietary names for each biosimilar could jeopardize patient safety, inhibit market competition and disrupt the current global naming system. GPhA is concerned that unsubstantiated claims regarding biosimilar nomenclature must not be used as an anti-competitive barrier to biosimilar development and commercialization.

Other producers of biologic reference products, namely Amgen and Genentech, publicly support the introduction of unique USAN for biosimilars in the US. In the meantime, GPhA members are considering an alternative proposal that might address some stakeholder concerns while remaining true to the fundamental principles of one USAN per molecule as the descriptor of the active ingredient.⁵ This would mean equal and consistent treatment for all biologics. Under this proposal, all biologic labels would carry a USAN plus a suffix that identifies the Biologics License Application (BLA) holder in the U.S. (e.g. Filgrastim Amgen, Filgrastim Teva). This convention would be implemented for all biologics in the US, including retroactive implementation for those biologics approved prior to the introduction of this convention. Company name as an identifier is a logical approach that avoids the use of abbreviations or

³ McCamish, Gallaher, Orloff “Biosimilar by Name and Biosimilar by Nature”, RPM Report, June 28, 2013

⁴ ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process. EU: Adopted by CMPM, December 1, 2004, CPMP/ICH/5721/03, date for coming into operation: June 2005; MHLW: Adopted 26 April 2005, PFSB/ELD Notification No. 0426001; FDA: Published in the Federal Register, Vol. 70, No. 125, June 30, 2005, p. 37861-37862.
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed 10 April 2012). Definition “Comparable: 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.”

⁵ WHO, “International Nonproprietary Names,” available at: <http://www.who.int/medicines/services/inn/en/> (accessed 25Feb14).

random codes that can be confusing and lead to medication errors. The convention would be used on all biological product packaging, labeling, advertising and promotional materials as defined by FDA; it should not preclude the (additional) use of brand names. And this approach does not preclude the use of brand names.

The above-described naming convention represents a compromise because GPhA has and still maintains that the current system for biologics naming includes sufficient and redundant means of product identification – brand name, National Drug Code (NDC) number and manufacturer. Note that GPhA members have endorsed and plan to implement the use of brand names for biosimilars.

Lastly, as a scientific matter, a biosimilar naming approach that maintains the same USAN is consistent with the fact that comparable or “highly similar” originator biologics produced by a change in a manufacturing process or facility share the same USAN as the pre-manufacturing change biologic.

GPhA advocates for consistency of all biologics with regard to naming as it is supported by science and is conducive to fair competition that will not only increase affordability and patient access but also stimulate innovation and investment in the next generation of originator biologics.

Potential Impact of State Regulations and Naming Conventions

In 2013, brand-backed legislation pertaining to the automatic substitution of interchangeable biological products was introduced in 19 states. These bills sought to add special notice and other administrative burdens at the pharmacy that could chill interchangeable biological product substitution. GPhA believes that unimpeded substitution is of critical importance in the very early stages of the emerging interchangeable biological product marketplace – and if legislation imposing barriers to substitution is passed in the states; the promise of cost savings and increased access for patients may never materialize.

1. How would new state substitution laws passed in 2013, or similar proposals pending in other states, affect competition expected to develop between biosimilar or interchangeable biologics and reference biologics? In the context of state substitution laws, what is the likely competitive impact of a biologic product being designated “interchangeable?”

A. Background: 2013 Laws

The brand-backed legislation pushed in 2013 included four key components:⁶

- Allows for the automatic substitution of FDA-approved interchangeable biological products for the prescribed reference product when certain conditions are met.

⁶ For example see PA SB 405:

<http://www.legis.state.pa.us/CFDOCS/Legis/PN/Public/btCheck.cfm?txtType=HTM&sessYr=2013&sessInd=0&billBody=S&billTyp=B&billNr=0405&pn=1554>

- Allows for the doctor to mark “Brand Necessary” or “Do not Substitute” on the prescription pad to prevent substitution.
- Requires the prescribing physician to be notified within a specified period of time of the substitution.
- Requires the pharmacy to keep a record of the substitution for a period of time that is generally longer than required for small molecules.

Most bills started off with these provisions, but North Dakota was the only state to pass the legislation in its entirety. Oregon, Utah, and Virginia passed legislation that included a sunset clause on physician notification. The Florida legislature amended the brand model bill, removing physician notification, so that the law mirrors current generic substitution laws. Other 2013 bills in Delaware, Illinois, Massachusetts, and Pennsylvania were not acted on in 2013.

Massachusetts introduced a bill independently, which only requires the pharmacist to place a record of the substitution in an interoperable electronic record keeping system that will come online in 2017.⁷

B. 2014 Laws-as of Feb 28, 2014

In the first few months of 2014, legislation concerning the substitution of interchangeable biological products has been introduced in six states – with varied approaches.

i. Washington⁸

This bill would allow for the substitution of FDA approved interchangeable biologics under certain circumstances, would allow for the doctor to prevent substitution, and requires the pharmacy to keep a record of the substitution for a period of time longer than small molecule substitution records. The word “notification” was changed to “communication.” The pharmacist must enter the name and manufacturer of the biological product that was dispensed (reference product or interchangeable) into an interoperable electronic health records system if one is in place or, if one is not in place, the pharmacist has ten days to communicate the name and manufacturer of the biological product dispensed to the prescribing physician. This legislation was rejected by the Legislature.

ii. Georgia⁹, Vermont¹⁰

These bills, like Florida in 2013, mirror current interchangeable pharmacy practice for each state. The bills allow for the substitution of FDA approved interchangeable biological products, allow for the prescribing physician to prevent substitution, and keep current record keeping practices in the individual states.

iii. New Jersey,¹¹ Indiana¹², Mississippi¹³

⁷ Mass. Gen. Laws Part I Title XVII, Chapter 118I Section 7.

⁸ Washington HB 2326: <http://apps.leg.wa.gov/documents/billdocs/2013-14/Pdf/Bills/House%20Bills/2326.pdf>

⁹ Georgia SB 370: <http://www.legis.ga.gov/Legislation/20132014/139373.pdf>

¹⁰ Vermont HB 837: <http://www.leg.state.vt.us/docs/2014/bills/Intro/H-837.pdf>

Bills introduced in these three states were similar to the bills pushed in 2013. After their introduction in Indiana and Mississippi, they were amended to look like the bill proposed in Washington’s so-called “compromise” legislation. Mississippi sent the bill to a study committee and Indiana’s bill passed both houses.

C. Effects on competition between interchangeable biological products and reference products

Carve out legislation is a common strategy brand companies use to shield their products from competition. Carve out legislation amends the pharmacy practice acts to add barriers to substitution such as notification, record keeping, and/or consent requirements to a class of drugs. These legislative pushes precede or coincide with patent expiry. Carve outs can be accomplished by requiring additional administrative burdens before or after substitution (such as notification¹⁴), written patient consent to substitution, or even requiring additional permission from the doctor at the point of substitution. Carve out legislation is scientifically and medically unnecessary, and chills substitution of FDA-approved interchangeable products.

Similar to carve out legislation for small molecules, the proposed interchangeable biologic state legislation creates a unique pharmacy practice specific to interchangeable biologics. This increases administrative burdens at the pharmacy and creates doubt about the safety and effectiveness of FDA-approved interchangeable products. There is no scientific or legislative reason for treating interchangeable biological products differently. The Biological Price Competition and Innovation Act (BPCIA) clearly states that interchangeable biological products “may be substituted **without the intervention of the healthcare provider...**”¹⁵ The FDA is aware of the complexity of these products, and interchangeable biological products and biosimilars will have to meet the rigorous safety standards set forth in the BPCIA to be approved.¹⁶ The BPCIA also states that an interchangeable biologic is not considered to have a “new active ingredient”; while a non-interchangeable biosimilar is considered to have a “new active ingredient”, making it clear that the interchangeable biologic should be substitutable like a generic drug.¹⁷

The impact of these tactics on health care costs should not be underestimated. In 2007 a Tennessee law required the prescriber be notified before a pharmacist could substitute epilepsy

¹¹ New Jersey AB 2477: http://www.njleg.state.nj.us/2014/Bills/A2500/2477_11.PDF

¹² Indiana SB 262: <http://iga.in.gov/static-documents/e/e/1/2/ee1292d4/SB0262.02.COMS.pdf>

¹³ Mississippi SB 2731: <http://billstatus.ls.state.ms.us/documents/2014/pdf/SB/2700-2799/SB2731IN.pdf>

¹⁴ See Mass. Gen. Laws Part I Title XVI Chapter 112 §12D

¹⁵ 42 USC §262(i)(3)

¹⁶ 42 USC §262(i)(2) and (3); 42 USC §262(k)(4).

¹⁷ Section 351(n) of the BPCIA, for example, only applies the “new active ingredient” special studies requirement under Section 505B to non-interchangeable biosimilar biologic products, as follows:

- (1) Non-Interchangeable Biosimilar Biologic Product. -- A biological product that is biosimilar to a reference product under section 351...that the Secretary *has not* determined to meet the standards described in subsection (k)(4) of such section for interchangeability with the reference product *shall be considered to have a new active ingredient* under this section.
- (2) Interchangeable Biosimilar Biologic Product. —A biologic product that is interchangeable with a reference product under section 351...*shall not be considered to have new active ingredient* under this section.

Emphasis added.

medications. In 2010 a fiscal note demonstrated the original bill cost the state's general fund \$4,878,400¹⁸ and resulted in a **29.4% increase in the use of brand name drugs** in the multi-source brand class. Requiring notification to the prescribing physician had demonstrably chilled substitution of FDA approved interchangeable drug products. Although the bills before statehouses in 2014 include language requiring post-dispensation notification, it is important to note that pharmacies are likely to create policies around notification provisions ensuring that any notification is made before dispensing an expensive product to minimize patient confusion and loss of pharmaceutical stock.

Unimpeded substitution is therefore imperative for increasing utilization of interchangeable medicines. As the Commissioner of the FDA recently stated:

“The 2010 law expressly states that a pharmacist or other dispenser may substitute an interchangeable biological product for the reference product without consulting the prescribing doctor. And this is important. Substitutability helped spur the growth of the generic drug industry at an earlier time and is similarly essential to help foster competition in the biological drug market. Ultimately, such competition will spur innovation, improve consumer choice and drive down medical costs.”¹⁹

This legislative push has also created doubt about the safety and effectiveness of biosimilars even before they are approved. For example, a legislator in Arizona expressed her understanding of the difference between reference biological and interchangeable biological products by representing the reference product with plush towels, and the interchangeable product with store-brand paper towels asking: “Which would you prefer?” A legislator in Indiana expressed his understanding of the difference between reference products and interchangeables by showing a picture of a St. Bernard and a Chihuahua, expressing that the two were biologically similar, and interchangeable for some purposes, “But wouldn’t you want to know which one you were taking home?” Lost in both discussions were the standards that the FDA is bound by to approve a biological product as interchangeable.²⁰ This is the impression left in the minds of lawmakers who, in order to increase patient access and balance budgets, need to pass legislation to encourage, rather than block, the use of safe, effective, and affordable biological treatments. Unfortunately, this confusion only serves to amplify the unfounded fears regarding biosimilar products even before even a single biosimilar has been licensed by the FDA and plays right in to

¹⁸ See Appendix A

¹⁹ Remarks by Food and Drug Administration (FDA) Administrator Margaret Hamburg at the GPhA Annual Meeting, Friday, February 22, 2013.

²⁰ 42 USC §262(k)(4)

(4) Safety standards for determining interchangeability

Upon review of an application submitted under this subsection or any supplement to such application, the Secretary shall determine the biological product to be interchangeable with the reference product if the Secretary determines that the information submitted in the application (or a supplement to such application) is sufficient to show that—

(A) the biological product—

(i) is biosimilar to the reference product; and

(ii) can be expected to produce the **same clinical result as the reference product** in any given patient; and

(B) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is **not greater than the risk of using the reference product without such alternation or switch**. (emphasis ours).

the hands of the market incumbents with large sales forces, aggressive tactics, and a head start in the minds of prescribing physicians.

3. What are the rationales behind new state proposals and laws for regulating FOB substitution? Which provisions are most important? Are some provisions redundant or otherwise unnecessary?

A. Background: The Rationale Behind the State Proposals

In 2013, the Biotechnology Industry Organization (BIO) released five principles,²¹ which these bills were based on:

- Substitution should occur only when the FDA has designated a biological product as interchangeable
- The prescribing physician should be able to prevent substitution
- The prescribing physician should be notified of the substitution
- The patient or the patient's authorized representative, should, at a minimum, be notified of the substitution
- The pharmacist and the physician should keep records of the substitution

GPhA supports four of the five principles as they are current pharmacy practice and strengthen the prescriber/pharmacist/patient relationship. These safeguards are critically important to maintaining confidence in state-level drug product selection practices. GPhA opposes the one principle that would undermine the pro-competitive and innovation driving purpose of including the interchangeability designation in the biosimilar pathway.

B. Special Physician Notification is Redundant

GPhA does not agree with the third principle: requiring the prescribing physician special notice of the substitution. BIO explains their rationale for this requirement:

Even though interchangeable biologics will be “expected” to produce the same clinical result, it remains the case that patients could react differently to an interchangeable biologic than if they were given the innovator product due to the complex nature of biologic products and how they work in the human body. In these circumstances, the treating physician must know that the products were substituted at the point of dispensing in order to appropriately assess a patient’s experience and further treatment options. Moreover, it is in the interest of public health to be advised of which biologic is being administered, as it will facilitate attribution to the proper product for adverse event reporting.

In all states, prescribers have the ultimate authority to determine whether it is appropriate for a pharmacist to substitute an interchangeable for a brand-named product when issuing a prescription by personally indicating, “Do no substitute,” “Brand Medically Necessary” or words of similar meaning. If there is any reason for concern about substitution, the prescriber will act accordingly.

²¹ <http://www.bio.org/sites/default/files/BIO-Principles-on-Substitution.pdf>

The FDA has been working with, approving, and monitoring biological products for decades and recognizes the complexity inherent in biological products. The BPCIA explicitly states that interchangeable biological products may be substituted without the intervention of the healthcare provider.²²

The pharmacy or PBM systems keep comprehensive records of every substitution including trade name, manufacturer, and NDC for billing purposes, therefore, a complete record for each patient exists and can be accessed as necessary.

Despite the inherent complexity of biological products – notification has never been a concern until now, coinciding with the BPCIA and expected competition. A brand manufacturer changes processes, a manufacturing plant, or a cell line and even though these changes could alter the efficacy of their medicines, prescriber notification has not been discussed. It is only now, when competition is entering the market, that there is an emphasis on prescriber notification.

4. Could an FDA publication concerning biologics and FOBs, comparable to the Orange Book, provide an authoritative listing of FOBs that are biosimilar to or interchangeable with reference biologics? Would such a publication facilitate substitution? Would such a publication need to be limited to interchangeable FOBs, or should it include both biosimilar and interchangeable FOBs?

A. An FDA publication concerning biologics would provide an authoritative listing of interchangeable biological products.

GPhA believes that an Orange Book-type listing of biological products that are interchangeable with reference products would provide an authoritative listing of biological products. The Orange Book itself has served as an authoritative list for years and many state pharmacy practice acts refer to the Orange Book as the definitive and comprehensive source for interchangeable drug products.²³ It also allows pharmacists and those creating formularies and Medicaid Prescription Drug Lists a one-stop reference to ensure patients receive the same clinical result at a lower cost.

To the extent that the states are still exploring the issue of interchangeable biological substitution, a definitive list of those products that are deemed interchangeable, would ease the transition to substitutability as envisioned by the BPCIA.

B. An “Orange Book” for biologics would facilitate substitution

²² 42 USC §262(i)(3).

²³ See WI Statute 450.13(1): Drug product or equivalent to be used. Except as provided in sub. (2), a pharmacist shall dispense every prescription using either the drug product prescribed or its drug product equivalent, if its drug product equivalent is lower in price to the consumer than the drug product prescribed, and shall inform the consumer of the options available in dispensing the prescription. In this section, "drug product equivalent" means a drug product that is designated the therapeutic equivalent of another drug product by the federal food and drug administration.

There is a need to know which products are interchangeable and which are biosimilar, and having one authoritative source produced by the FDA would facilitate appropriate substitution. This is because many states reference the Orange Book in their state substitution laws, and many more implicitly rely on the Orange Book through third party databases at the pharmacy level. All of the state level substitution bills allow for the substitution of interchangeable biological products *only* if the FDA approves them as interchangeable. Having one definitive source of those medicines would allow for pharmacists to easily determine which products are interchangeable and which are biosimilar. The FDA is presently considering instituting a reference book (the so called Purple Book) that could address this matter.

C. To Provide a Comprehensive Resource, the FDA Publication Should Include Both Biosimilars and Interchangeable Biological Products

An Orange Book for biologic products should include both biosimilars and interchangeable biological products. This would provide consistency and streamline processes for payors, pharmacists, pharmacy and therapeutics committees, and those making prescription drug lists and formularies.

5. Does the potential for many different state laws regulating FOBs affect the prospects for the development of FOBs? Does the answer differ between biosimilar versus interchangeable biologic products?

A. State Substitution Laws Have the Potential to Affect Development of Interchangeable Biological Products

If state substitution laws diminish the potential for substitution, and create enough doubt about the safety and effectiveness of both biosimilars and interchangeable biological products – then future development of those products may be affected. For example, if states pass onerous carve out language that requires additional notification, patient consent, or pre-dispensing consent by the physician – then substitution rates may be so low for interchangeable biological products manufacturers might not make the financial investment²⁴ to obtain interchangeability. That is, unimpeded substitution ensures a high degree of utilization, enabling a market share even without a marketing and sales force detailing these products. Without unimpeded substitution – the economic incentives to meet those stringent standards may not materialize, particularly for organizations that lack sales and marketing teams.

B. Interchangeable Biological Products are More Vulnerable to Variations in State Law

This legislation and lack of legislators’ understanding of this highly complicated and scientific area, creates doubt about the safety and effectiveness of all biosimilars. Since this legislation adds barriers only to the automatic substitution of interchangeable biological products, they are the most vulnerable to legislation variations.

²⁴ As FDA has not released final guidance on interchangeability – we do not currently know what is required to obtain the interchangeability standard.

6. Would it be helpful to develop a model state substitution biosimilar law? If so, what provisions should the law include? Should state laws coordinate their guidance with provisions in the BPCIA and guidance from FDA?

GPhA and our allies have advocated for substitution laws to mirror those currently in existence for interchangeable small-molecules. This provides continuity and consistency in pharmacy practice, while following the definitions set out by the BPCIA. This is a highly scientific, complex, and confusing issue. As biologic medicine is not a usual area for their review, misinformation can easily be spread and unfortunately influence proposed legislation, the generic industry spends much time during the swift-moving state legislative process correcting the record and explaining half-truths and allaying fears about all biological products before being able to make our case for legislation without additional barriers to substitution. If an independent agency created model legislation based on current practice, it would provide legislators with an unbiased and educated alternative to current legislative trends.

Conclusion

GPhA recommends that all biologics should share the same USAN as the RPP. This is the same standard as comparable brand products produced by a change in a manufacturing process or facility, which share the same USAN as the original RPP. Fewer barriers and increased access to biosimilar products will increase the affordability of these life-saving, yet frequently costly, products.

Sincerely,


Ralph G. Neas
President and CEO