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September 21, 2018

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2018-N-2689: Facilitating Competition and Innovation in the Biological Products Marketplace; Public Hearing; Request for Comments

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit these comments in response to the Food and Drug Administration's (FDA's or the Agency's) request for comments on "Facilitating Competition and Innovation in the Biological Products Marketplace."[1] PhRMA represents the country's leading innovative biopharmaceutical research and biotechnology companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. Since 2000, PhRMA member companies have invested more than $600 billion in the search for new treatments and cures, including an estimated $71.4 billion in 2017 alone.

PhRMA participated in the public hearing and is pleased to supplement our comments. We appreciate the Administration's and FDA's efforts to promote innovation and competition in America's health care system and specifically, the marketplace for biological products. PhRMA supported the enactment of the Biologics Price Competition and Innovation Act (BPCIA), has actively participated in FDA's implementation activities (including negotiations with respect to the Biosimilars User Fee Act (BsUFA) and its recent reauthorization to help assure timely approval of biosimilars), and supports continued evolution of the biosimilars pathway. As America's health care system evolves, biosimilars are anticipated to play a critical role in constraining prescription drug cost growth by reducing spending on biologics. This is on top of cost savings from generics, which now represent 90 percent of all medicines dispensed to patients.[2] PhRMA urges FDA to take appropriate steps to foster a scientifically rigorous regulatory policy for biosimilar products that can bring these important medications to patients and maintain incentives for innovation; we look forward to working with the Administration and FDA on further policy development efforts.

Below, PhRMA addresses the following specific issues identified either in the *Federal Register* notice, the Biosimilars Action Plan, and/or the public hearing.

1. PhRMA strongly supports FDA's application of an "umbrella exclusivity" policy for biological products. We believe that umbrella exclusivity is necessary for policy

[1] 83 Fed. Reg. 35,154 (July 25, 2018).

[2] IMS Institute for Healthcare Informatics, *Medicines Use and Spending in the U.S. A Review of 2016 and Outlook to 2021* (May 2017).

reasons, dictated by the statute and legislative intent, and unrelated to patent issues (Question 8 in *Federal Register* notice).

2. PhRMA supports FDA's use of appropriate data-sharing agreements to facilitate harmonized development advice to biosimilar developers and FDA's adoption of analogous bridging study standards for use of non-U.S.-licensed comparators in development programs for reference products and biosimilar products. We do not object to FDA's use of public information as the basis for scientifically sound waivers of bridging study requirements, but FDA's reliance on trade secret information about the manufacturing of a non-U.S.-licensed comparator and corresponding U.S.-licensed reference product to waive bridging study requirements would raise serious legal issues (Question 5).

3. PhRMA urges FDA to promptly issue substantially revised guidance on the transition provisions of the BPCIA, under which approved new drug applications (NDAs) for biological products will be deemed to be biologics license applications (BLAs) on March 23, 2020. In lieu of FDA's 2016 proposal to extinguish unexpired Hatch-Waxman and pediatric exclusivity for transitioning NDAs and deny them any reference product exclusivity, FDA should apply granted exclusivity and the Hatch-Waxman patent provisions through the term of the last-expiring Orange Book-listed patent. Further, to increase efficiency and reduce regulatory burden, FDA should allow transitional applications that are pending on March 23, 2020 to retain their status until final approval, when they will be deemed to be BLAs. FDA also should address several important issues for transitional NDAs that are not mentioned in the draft guidance (Goal 4 in *Federal Register* notice).

4. PhRMA supports FDA's efforts to enhance the Purple Book and offers three recommendations to achieve this goal. First, to enable informed investment decisions by both biosimilar sponsors and innovators, the Purple Book should state FDA's commitment to publish prompt reference product exclusivity determinations upon BLA approval. We also recommend publication of information on orphan-drug and pediatric exclusivity in the Purple Book. Second, to promote confidence in biosimilar and interchangeable products, the Purple Book should clarify that an interchangeability determination reflects FDA's judgment that an interchangeable biosimilar may be substituted for the reference product, not another biosimilar product. This clarification could be made in a glossary of terms that includes definitions of biosimilarity and interchangeability. Finally, adding patent information to the Purple Book is not possible under current law and would strain FDA resources (Question 2).

5. PhRMA supports expanding biosimilar labeling to include a previously-protected condition of use when the relevant protection expires as well as development of a clear process for these additions. We urge FDA to respect protected uses by refraining from public discussion or disclosure of its deliberations regarding biosimilarity as to a protected condition of use until the protection expires (Question 7).

6. PhRMA looks forward to FDA's publication of further guidance on the demonstration of analytical similarity for biosimilars. We support FDA's goal of reducing the cost of analytical studies for biosimilars while ensuring appropriate sampling and analysis of

the reference product from a scientific perspective. PhRMA also encourages FDA to foster innovation in biologics development by taking a more risk-based approach to the evaluation of critical quality attributes (CQAs) and associated product specifications, instead of creating a CQA index (Question 4).

7. PhRMA supports the development of appropriate state-of-the-art tools to streamline development of both innovative and biosimilar products. PhRMA is supportive of the development of methods such as *in silico* modeling and simulation, and we look forward to working with FDA to enable faster and more efficient drug development using these tools and technologies for both biosimilars and innovator drugs. However, PhRMA believes that these methods currently have limitations and that these approaches, in their current state, lack the precision and specificity to replace a clinical showing of biosimilarity, and in particular, of immunogenicity (Goal 1).

8. PhRMA urges FDA to continue to approve reference product BLAs and supplemental BLAs that meet the statutory requirements for approval and accordingly, recommends that FDA preserve flexibility when it comes to changes in manufacturing processes of innovator biologics in accordance with section 351(a) of the Public Health Service Act (PHSA) (Question 6).

9. PhRMA supports FDA's efforts to address access to reference product samples within the scope of its authority (Goal 6).

10. We encourage FDA to recognize the important role of the citizen petition process in raising critical scientific, policy, and legal issues for FDA's consideration and to rely upon accurate data in assessing claims that the vast majority of citizen petitions lack merit (Goal 6).

11. PhRMA supports FDA's continued efforts to educate stakeholders about biosimilars (Question 3).

I. Umbrella Exclusivity Is Essential to Preserve the Value of Reference Product Exclusivity and Encourage Investment in Innovation (Question 8).

PhRMA strongly supports FDA's application of an "umbrella exclusivity" policy for biological products.[3] As FDA explained in the *Federal Register* notice, with an umbrella exclusivity policy, "a biological product that would not be eligible for a new period of exclusivity under section 351(k)(7)(C) [of the PHSA] would nevertheless be protected for the duration of the exclusivity period for a previously approved reference product."[4] Importantly, an umbrella policy would not extend exclusivity beyond the original period. An umbrella exclusivity policy is critical from a public policy perspective, mandated by the statute, and most consistent with the legislative history of the BPCIA. Further, the BPCIA patent provisions are irrelevant to whether umbrella exclusivity applies, as Congress intended reference product exclusivity to run concurrently with patent protection, not for one to substitute for the other.

[3] *See* 83 Fed. Reg. at 35,156.

[4] *Id*.

An umbrella policy is necessary to maintain the value of reference product exclusivity and foster the investments in research and development needed to support continued improvements to, and further study of, biologics to meet patient needs. Without an umbrella policy, a product change that is ineligible for its own reference product exclusivity—for example, a new indication or route of administration—would be protected by no reference product exclusivity at all. A biosimilar applicant could immediately obtain approval for that changed product or new use, even before it could obtain approval of a biosimilar of the original reference product. This would effectively eviscerate the exclusivity for the first-licensed product. In this way, the lack of an umbrella policy would discourage additional R&D investments for new indications and otherwise improved biological products and expanded treatment options for patients.

Similar considerations led FDA to adopt an umbrella policy in the context of small-molecule products. The Agency recognized that without an umbrella policy, a manufacturer that receives new chemical entity exclusivity "could not make improvements in the drug, e.g., by making a new dosage form of the drug, without destroying the value of its exclusivity" because "once approved, the new dosage form would become a new drug product that an [abbreviated new drug application] could copy, without being subject to the exclusivity covering the original drug product."[5] FDA concluded that the legislative purpose of the Hatch-Waxman Amendments compelled the adoption of an umbrella policy because Congress did not "intend[] the exclusivity provisions to discourage innovators from making improvements in their drug products."[6]

Congress had parallel goals in drafting section 351(k)(7), which implicitly mandates umbrella exclusivity. Section 351(k)(7) provides that reference product exclusivity runs from the "date on which the reference product was first licensed under subsection (a)" of section 351.[7] This text thus reflects that there will be subsequent licensures with respect to a biological product. As FDA has recognized, section 351(k)(7)(C) further indicates that the dates of approval of supplements and the subsequent applications described in section 351(k)(7)(C)(ii) are not first licensure dates.[8] This provision thus implies that the first licensure date for such supplements and subsequent applications is the same as the first licensure date for the previously approved biological product. Under this framework, even where a subsequent product's approval is not considered a first licensure, the subsequent product should be entitled to any remaining exclusivity for the original product under an umbrella policy.

Section 7002(h) of the BPCIA contains even clearer evidence that Congress intended for umbrella exclusivity to apply to biologics. This provision, reprinted below, addresses the relationship between reference product exclusivity and orphan-drug exclusivity:

> If a reference product, as defined in section 351 of the [PHSA] . . . has been designated under section 526 of the Federal Food, Drug,

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[5] Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,897 (July 10, 1989).

[6] *Id*.

[7] PHSA § 351(k)(7)(A) & (B), 42 U.S.C. § 262(k)(7)(A) & (B).

[8] *See* FDA, Draft Guidance for Industry, *Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act*, at 3 (Aug. 2014) ("A biological product submitted for licensure under section 351(a) of the PHS Act (a 351(a) application) may be eligible for a period of exclusivity that commences on the date of its licensure unless its date of licensure is not considered a date of first licensure because it falls within an exclusion under 351(k)(7)(C)."); PHSA § 351(k)(7)(A) & (B), 42 U.S.C. § 262(k)(7)(A) & (B).

> and Cosmetic Act . . . for a rare disease or condition, a biological product seeking approval for such disease or condition under subsection (k) of such section 351 as biosimilar to, or interchangeable with, such reference product may be licensed by the Secretary only after the expiration for such reference product of the later of—
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> (1) the 7-year period described in section 527(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360cc(a)); and
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> (2) the 12-year period described in subsection (k)(7) of such section 351.[9]

This provision only has effect if umbrella exclusivity applies. Specifically, the provision cannot be interpreted to speak to the situation where the "first licensure" of the reference product is for the orphan indication; in this case, the provision would be superfluous, because the twelve-year reference product exclusivity period always exceeds the seven-year orphan-drug exclusivity period. The Supreme Court has recognized that one of the "most basic interpretive canons" is that "[a] statute should be construed so that effect is given to all its provisions, so that no part will be inoperative or superfluous, void or insignificant."[10] Accordingly, the provision must address situations where a subsequent approval of the reference product is for an orphan-protected indication that (as a new indication) does not qualify for its own period of reference product exclusivity under section 351(k)(7)(C)(ii)(I). In other words, the provision addresses situations where the seven-year orphan-drug exclusivity period might extend for longer than the unexpired portion of the twelve-year reference product exclusivity period. This scenario would occur only if the orphan indication is covered by the remainder of the original product's reference product exclusivity period under an umbrella policy.[11] If the statute did not contemplate umbrella exclusivity, this provision would be unnecessary, because the subsequent orphan indication would have no protection from reference product exclusivity.

Umbrella exclusivity also is necessary to achieve the legislative purpose of reference product exclusivity; i.e., to "preserve incentives for innovation" by "ensur[ing] that biosimilar applications that rely on the safety and efficacy record of existing biologic products will not be permitted to enter the market for 12 years following the approval of the innovator product."[12] Failure to recognize umbrella exclusivity would prevent accomplishment of this statutory purpose. For example, a supplemental BLA or new BLA seeking approval of the first-licensed product in a new use will likely not include information on basic toxicology and other issues specific to the molecule, but instead would focus on efficacy in the new use. If a biosimilar could

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[9] BPCIA § 7002(h), Pub. L. No. 111-148, 124 Stat. 119, 821 (2010).

[10] *Corley v. United States*, 556 U.S. 303, 314 (2009) (internal quotations and citations omitted).

[11] *See* Donald O. Beers & Kurt R. Karst, *Generic and Innovator Drugs: A Guide to FDA Approval Requirements* § 13.04[A][1], at 13-17 n.66 (8th ed., 2017 supp.) (observing that section 7002(h) "appears to anticipate a scenario in which a supplement to an approved BLA approved for a rare disease or condition is covered by any 'umbrella' exclusivity extending from the approval of the original BLA, and the period of orphan drug exclusivity extends beyond the expiration of reference product exclusivity").

[12] 155 Cong. Rec. E687, E688 (Mar. 17, 2009) (statement of Rep. Eshoo); 154 Cong. Rec. E401, E402 (Mar. 13, 2008) (same).

rely on that supplemental BLA or new BLA, it would also be relying indirectly on safety and efficacy data that supported first licensure. Such reliance before the expiration of the reference product exclusivity period for the first licensed product thus would be inconsistent with the legislative purpose of reference product exclusivity. As in the small molecule context, an umbrella policy is necessary to effectuate this legislative purpose because Congress did not "intend[] the exclusivity provisions to discourage innovators from making improvements in their drug products."[13]

Some have argued that the statute precludes umbrella exclusivity because it provides that the provisions conferring exclusivity "shall not apply" to FDA's approval of supplements and certain subsequent applications.[14] Not only does this proposed interpretation not square with 351(k)(7) of the PHSA and section 7002(h) of the BPCIA and the legislative purpose of reference product exclusivity, but it also departs from Congressional intent in enacting the first licensure provision.[15] Congress intended to preclude these applications from receiving a *separate period* of reference product exclusivity. For example, Senator Kennedy explained Congress's objective in crafting section 351(k)(7): to ensure that the "*12 years* of exclusivity applies only to products that are analogous to a 'new chemical entity'" and to preclude subsequent applications from "generat[ing] a new 12 years of exclusivity."[16] He further noted that, in the version of the bill then under consideration, "we used the phrase 'first licensed' to make clear that 12 years of exclusivity applied solely to the initial approval of a product, not to subsequent minor modifications" and committed to further sharpen the language to achieve this objective.[17] As in the Hatch-Waxman context, there is no evidence that Congress intended the BPCIA to discourage innovators from developing product changes or studying new uses to benefit patients by denying such changes any remaining reference product exclusivity for the original product. Indeed, the Association for Accessible Medicine's predecessor, the Generic Pharmaceutical Association (GPhA), contemporaneously stated that language in both the House and Senate biosimilars legislation—which included section 351(k)(7)(C)—"would give a *minimum* of 12 years of market exclusivity to brand biologics."[18] PhRMA urges FDA to uphold Congressional intent and promote innovation by applying an umbrella policy for biological products.

Finally, the BPCIA patent framework is not relevant or significant in considering FDA's question on whether umbrella exclusivity should apply.[19] Unlike in the Hatch-Waxman context,

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[13] 54 Fed. Reg. at 28,897.

[14] PHSA § 351(k)(7)(C), 42 U.S.C. § 262(k)(7)(C).

[15] *Cf. Hi-Tech Pharmacal Co. v. FDA*, 587 F. Supp. 2d 13, 22 (D.D.C. 2008) (upholding an FDA interpretation of section 505A of the Federal Food, Drug, and Cosmetic Act (FDCA) that "is the natural meaning in light of the text, structure, and purpose of section 10 of the [Best Pharmaceuticals for Children Act] and its interaction with" the FDCA's exclusivity and forfeiture provisions); *see generally Abramski v. United States*, 134 S. Ct. 2259, 2267 (2014) (a court must "interpret the relevant words not in a vacuum, but with reference to the statutory context, structure, history, and purpose" (internal quotation marks omitted)).

[16] Statement of Sen. Edward M. Kennedy on the Biologics Price Competition and Innovation Act (June 27, 2007).

[17] *See id.*

[18] Letter from Kathleen Jaeger, President & CEO, GPhA, to Pres. Obama (Oct. 27, 2009) (emphasis in original).

[19] *See* 83 Fed. Reg. at 35,156.

reference product exclusivity generally is not linked to the patent framework for biologics,[20] and the statute does not contemplate that FDA will consider the sufficiency of patent rights in administering its reference product exclusivity provisions or in licensure decisions. Indeed, Congress intended for the reference product exclusivity provision to operate independent of patent protection to reward investment in biotechnological innovation by providing certainty that innovators would have sufficient time to recoup their research and development investments before biosimilar competition.[21] As Rep. Anna Eshoo, the main sponsor of BPCIA in the House of Representatives, explained, data exclusivity is particularly necessary for biologics because "biosimilars—unlike generic drugs—will not be chemically identical to the reference product and will be less likely to infringe the patents of the innovator."[22] Similarly, during the legislative process, FDA and the U.S. Department of Health and Human Services urged Congress that biosimilars legislation should include "a significant period of market and/or data exclusivity, independent from any patent protections that might be applicable to the product, to ensure continued innovation."[23] An umbrella policy is essential to enable reference product exclusivity to play the vital, intended role of providing a reliable incentive for investment in research and development of innovative biological products.[24]

II. PhRMA Supports FDA Taking Appropriate Steps to Facilitate Multinational Development Programs Including Non-U.S.-Licensed Comparators (Question 5).

FDA noted in the *Federal Register* notice that a "351(k) applicant may, with adequate scientific justification, use a non-U.S.-licensed comparator product in certain studies submitted to support licensure of a proposed biosimilar product."[25] Given that, under the PHSA, biosimilarity and interchangeability must be shown to the "reference product," i.e., "the single biological product licensed under subsection (a)" of section 351 of the PHSA,[26] FDA expects

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[20] *Cf.* FDCA §§ 505(c)(3)(E)(ii) & (j)(5)(F)(ii), 21 U.S.C. §§ 355(c)(3)(E)(ii) & (j)(5)(F)(ii) (in the small-molecule context, providing for extension of the 30-month stay by "such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application" that qualifies for new chemical entity exclusivity if a patent infringement action is filed "during the one-year period beginning forty-eight months after the date of approval of the subsection (b) application").

[21] *See Biologics and Biosimilars: Balancing Incentives for Innovation, Hearing Before the Subcomm. on Courts and Competition Policy of the H. Comm. on the Judiciary*, 111th Cong. 11 (July 14, 2009) (statement of Rep. Eshoo) ("I'm proposing to . . . preserv[e] the existing incentives for innovators by maintaining a 12-year period of concurrent data protection as a 'backstop' to existing patent protections."); *Senate Panel Passes Biogenerics Bill; Still Working On Changes*, FDA WEEK (June 29, 2007) (noting that, in commenting about the bill that formed the backbone of the BPCIA, Sen. Kennedy indicated that he and Sens. Hatch, Clinton, and Enzi "agreed to the bill's clear-cut 12 years of brand exclusivity because, although many different approaches were discussed, the 12 years gave certainty")

[22] 155 Cong. Rec. E687, E688 (Mar. 17, 2009); 154 Cong. Rec. E401, E402 (Mar. 13, 2008).

[23] Letter from Frank M. Torti, M.D., M.P.H., Principal Deputy Comm'r and Chief Scientist, FDA, to Hon. Frank Pallone Jr., Chairman, Subcomm. on Health, U.S. House Comm. on Energy & Commerce, at 11-14 (Sept. 18, 2008); Letter from Michael O. Leavitt, Sec'y of Health and Human Services, to Hon. Edward M. Kennedy, Chairman, U.S. Senate Comm. on Health, Education, Labor, and Pensions, at 2 (June 26, 2007).

[24] An umbrella policy also is essential to ensure consistency with the United States' international obligations with regard to providing regulatory data protection for pharmaceutical products. *See, e.g.*, Agreement on Trade-Related Aspects of Intellectual Property Rights, at Art. 39(3).

[25] 83 Fed. Reg. at 35,156.

[26] PHSA § 351(i)(4), 42 U.S.C. § 262(i)(4).

biosimilar applicants to submit data that "establish an acceptable bridge to the U.S.-licensed reference product."[27] The Agency requested comments on "[w]hat additional steps . . . FDA [can] take to facilitate multinational development programs that may include non-U.S.-licensed comparators, to help support development of biosimilar products[.]"[28] Further context for FDA's request comes from Commissioner Gottlieb's announcement, one week before publication of the *Federal Register* notice, that FDA is "actively exploring whether data sharing agreements could . . . facilitate the increased use of non-U.S.-licensed products in certain studies to support an application under Section 351(k)."[29]

PhRMA supports FDA's use of appropriate data-sharing agreements to expedite drug and biologic development, including for biosimilars, by enabling regulators in different jurisdictions to provide harmonized development advice to the applicant regarding appropriate studies to satisfy multiple regulators. Further, we support FDA's adoption of analogous bridging study standards when non-U.S.-licensed comparators are used in development programs for reference products and biosimilar products.

PhRMA is concerned, however, by the suggestion that FDA would waive bridging study requirements based on non-public information about the relationship between a non-U.S.-licensed comparator and the reference product.[30] We do not object to waiving bridging study requirements if the biosimilar applicant can demonstrate—through publicly available information—that the non-U.S.-licensed product has the same drug substance, dose, dosage form, and route of administration as the U.S.-licensed reference product and is produced by the same manufacturer in the same facility using the same cell line. Indeed, the statute recognizes that a biosimilar application may include information such as "publicly-available information with respect to the reference product."[31] But in cases where the information that would form the basis for a waiver is trade secret or confidential commercial information of the innovator, FDA's disclosure of such information to a biosimilar developer—either explicitly or implicitly through waiver of bridging study requirements—would raise serious issues under federal law and the Takings Clause of the Fifth Amendment of the U.S. Constitution.[32]

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[27] FDA, Guidance for Industry: *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, at 8 (April 2015) ("As a scientific matter, the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that directly compare all three products (i.e., the proposed biosimilar product, the U.S.-licensed reference product, and the non-U.S.-licensed comparator product), and is likely to also include bridging clinical PK and/or PD study data for all three products.").

[28] 83 Fed. Reg. at 35,156.

[29] FDA, Remarks from FDA Comm'r Scott Gottlieb, M.D., as Prepared for Delivery at the Brookings Inst. on the Release of the FDA's Biosimilars Action Plan (July 18, 2018), *available at* https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm613881.htm.

[30] *See, e.g.*, Remarks from FDA Comm'r Scott Gottlieb, M.D., at Politico Pro Summit, at 4:12-5:05 (July 17, 2018) ("One of the things we're looking at doing is allowing European products to be used as the reference standard for biosimilar products . . . in cases where we know . . . [that the U.S. and European] products are manufactured in the same facility but the knowledge of that might constitute commercial confidential information, so we're looking at whether or not we can have data sharing agreements in place with our European regulatory authorities and we can use that knowledge to allow biosimilar sponsors to use the European product as the reference listed product . . ."), *available at* https://www.politico.com/video/2018/07/17/170617-fda-full-067139.

[31] PHSA § 351(k)(2)(A)(iii), 42 U.S.C. § 262 (k)(2)(A)(iii).

[32] *See, e.g.*, U.S. CONST. amend. V ("[N]or shall private property be taken for public use, without just compensation.").

Nonpublic details about whether the U.S.-approved reference product and foreign-approved comparator products are the same—e.g., the cell line used, the release specifications, etc., at particular manufacturing sites and for particular markets—likely constitute trade secrets because they would reveal commercially valuable elements of the manufacturing process.[33] Moreover, FDA's regulations generally prohibit the disclosure of "[m]anufacturing methods or processes, including quality control procedures," including after approval of a BLA, as well as trade secret information more generally.[34] The Federal Trade Secrets Act (FTSA) further makes it a criminal offense for a federal employee to improperly disclose trade secrets obtained in the course of employment.[35]

Accordingly, these provisions would bar FDA from disclosing the innovator's manufacturing process-related information in the agency's possession to biosimilar developers, even if that disclosure is made indirectly (for example, by waiving the requirement for bridging studies). This type of detailed manufacturing information is not discernible from FDA's prior public determination that the reference product is safe, pure, and potent.[36] A waiver by FDA of the requirement for bridging studies based upon the agency's knowledge of the innovator's trade secrets therefore cannot fairly be characterized as anything other than a disclosure of those trade secrets. Moreover, FDA's disclosure or other use of the innovator's manufacturing-related trade secrets is not contemplated by the BPCIA because, as FDA has recognized previously, a

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[33] 21 C.F.R. § 20.61(a) (defining a trade secret as "any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product or either innovation or substantial effort. There must be a direct relationship between the trade secret and the productive process."). Further, the Uniform Trade Secrets Act defines a trade secret as:

> [I]nformation, including a formula, pattern, compilation, program, device, method, technique, or process, that:
>
> (i) derives independent economic value, actual or potential, from not being generally known to, and not being readily ascertainable by proper means by, other persons who can obtain economic value from its disclosure or use; and
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> (ii) is the subject of efforts that are reasonable under the circumstances to maintain its secrecy.

Nat'l Conf. of Comm'rs on Uniform State Laws, Uniform Trade Secrets Act with 1985 Amendments § 1(4), *available at* http://www.uniformlaws.org/shared/docs/trade%20secrets/utsa_final_85.pdf.

[34] 21 C.F.R. § 601.51(f)(1); 21 C.F.R. § 20.61(c).

[35] *See* 18 U.S.C. § 1905. Additionally, the Supreme Court has held that "any disclosure that violates § 1905 is 'not accordance with law' within the meaning of 5 U.S.C. § 706(2)(A)" and therefore may be the basis for an action under the Administrative Procedure Act—commonly called a reverse-Freedom of Information Act (FOIA) suit. *Chrysler Corp. v. Brown*, 441 U.S. 281, 318-19 (1979); *see, e.g.*, *CNA Fin. Corp. v. Donovan*, 830 F.2d 1132, 1133 n.1 & 1151 (D.C. Cir. 1987) ("[T]he scope of the [Federal Trade Secrets] Act is at least co-extensive with that of Exemption 4 of FOIA."). Section 301(j) of the FDCA generally prohibits the "using by any person to his own advantage, or revealing" of trade secrets acquired under specified sections of the FDCA (including section 505) and may apply to biologics license applications by virtue of section 351(j) of the PHSA.

[36] *Cf.* Letter from Steven K. Galson, M.D., M.P.H., FDA, to Kathleen M. Sanzo, Stephan E. Lawton, and Stephen G. Juelsgaard re: Docket Nos. FDA-2004-P-0339, FDA-2003-P-0003, FDA-2004-P-0214, and FDA-2004-N-0059, at 6 (May 30, 2006) (FDA has stated that "[r]eliance on FDA's finding or conclusion that an approved drug is safe and effective does not involve disclosure to the ANDA or 505(b)(2) applicant — or to the public — of the data in the listed drug's NDA. Instead, it permits the ANDA or 505(b)(2) applicant to rely on the fact that FDA found a drug product with certain characteristics to be safe and effective .... ").

"biosimilar applicant does not rely on any manufacturing process information submitted for the reference product."[37] FDA's explicit or implicit disclosure of the innovator's trade secrets (i.e., that the non-U.S.-licensed comparator is the same as the U.S.-licensed reference product) to a biosimilar applicant as part of an adjustment of approval requirements to facilitate approval of a biosimilar application would entail actual use of those trade secrets in a manner inconsistent with the PHSA, FDCA, FTSA, and FDA regulations.

Such effective disclosure and use of the reference product sponsor's trade secrets to waive bridging studies for a biosimilar application is prohibited by the Takings Clause without just compensation.[38] As noted, the above laws, taken together, provide an "explicit assurance" that FDA will not use or disclose a reference product sponsor's manufacturing process-related trade secrets that are in the agency's possession.[39] This assurance forms the basis for a "reasonable investment-backed expectation" that the reference product sponsor's trade secrets will not be used or disclosed without authorization, an expectation with which FDA's proposed approach would interfere.[40] FDA's effective disclosure of the trade secrets therefore would trigger the key element of a prohibited "taking" in the absence of just compensation.[41] PhRMA urges FDA to carefully consider these legal issues with the described proposal.

III. FDA Should Promptly Issue Substantially Revised Guidance on Transition Products (Goal 4).

FDA requested input on "[h]ow the Agency can . . . [p]rovide additional scientific or regulatory clarity regarding FDA's regulation of biological products[.]"[42] PhRMA seeks clarification of FDA's plans for implementing the transition provisions of the BPCIA, under which approved NDAs for biological products will be deemed to be BLAs on March 23, 2020.[43]

FDA published draft guidance on this topic in March 2016, but the Agency has not finalized that guidance.[44] In comments on the draft guidance, we expressed concern with FDA's proposal to extinguish unexpired Hatch-Waxman and pediatric exclusivity for transitioning NDAs and deny them any reference product exclusivity.[45] The Agency's proposal is inconsistent with the BPCIA in at least four respects. First, it denies sponsors their right—as provided by section 7002(e)(2) of the BPCIA—to choose to submit an NDA for a transition product until

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[37] Letter from Janet Woodcock, M.D., to Timothy C. Hester, Covington & Burling LLP, re: Docket No. FDA-2012-P-0317, at 14 (Sept. 23, 2016). Instead, the biosimilar applicant "must generate and submit its own information to establish that the manufacturing process for the biosimilar product is acceptable." *Id*.

[38] *See Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1001-04, 1013-14 (1984).

[39] *Id*. at 1011.

[40] *Id*. at 1010-12.

[41] *See id*. at 1004.

[42] 83 Fed. Reg. at 35,156.

[43] BPCIA, § 7002(e)(4), 124 Stat. at 817 (2010).

[44] FDA, Draft Guidance for Industry, *Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009* (Mar. 2016) (Transition Products Draft Guidance).

[45] *See* PhRMA, Comments to Docket No. FDA-2015-D-4750, at 2, 4-14 (May 13, 2016) (PhRMA Comments on Transition Products Draft Guidance) (addressing Transition Products Draft Guidance, lines 190-91 & 201-06).

March 23, 2020.[46] Second, it overlooks the flexibility inherent in Congress's use of the word "deemed" in providing that an NDA for a transition product will be "deemed to be" a BLA on the transition date.[47] Third, FDA's proposed approach would overstep the Agency's authority by adding to the statute's exclusive list of exceptions to eligibility for reference product exclusivity.[48] Finally, FDA's proposal to strip transition product applications of unexpired pediatric exclusivity on the transition date conflicts with the legislative intent behind section 351(m) of the PHSA, which expressly provides pediatric exclusivity for BLAs.[49] FDA's proposal to extinguish unexpired exclusivity also would raise serious issues under the Takings Clause with respect to NDA holders' property rights in their trade secrets and in regulatory exclusivity itself.[50] In addition to these legal concerns, the Agency's proposed approach would significantly harm incentives for innovation.

As noted in our comments on the draft guidance, the statute allows FDA to adopt an alternative approach in which already-granted exclusivity would remain in place and the Hatch-Waxman patent provisions would apply through the term of the last-expiring Orange Book-listed patent for a drug.[51] This approach would be consistent with the statutory provision allowing sponsors of innovative transition products to choose between the NDA and BLA pathways—and their corresponding rights—until the transition date and with the flexibility conferred by Congress's use of the word "deemed."

PhRMA also raised concerns with FDA's proposal to require transitional NDAs and supplemental NDAs that remain pending on the transition date to be withdrawn and resubmitted as BLAs or supplemental BLAs.[52] To increase efficiency and reduce regulatory burden, FDA instead should allow these applications to retain their status until final approval, when they will be deemed to be BLAs or supplemental BLAs.[53] Like our above exclusivity proposal, this approach would effectuate a sponsor's statutory right to choose between the NDA and BLA pathways *until* the transition date.

Finally, PhRMA encouraged FDA to address several important issues for transitional NDAs that are not mentioned in the draft guidance, including the following:

- Whether NDAs for transition products will be deemed to be BLAs under section 351(a) or section 351(k) of the PHSA;

- Whether—on the transition date—transition products will be added to the Purple Book;

[46] PhRMA Comments on Transition Products Draft Guidance, at 6.

[47] *Id*. at 6-7.

[48] *Id*. at 7-8.

[49] *Id*. at 8-9.

[50] *Id*. at 9-12.

[51] *Id*. at 13-14.

[52] *Id*. at 14-18.

[53] *Id*. at 16-18.

- The administrative procedures that will be involved in the deeming of an NDA to be a BLA on the transition date;

- The technical requirements that will apply to sponsors, manufacturers, and/or distributors of transition products after the transition date; and

- How FDA intends to interpret the "first licensure" exception for new BLAs for transition biological products.[54]

We urge FDA to provide prompt clarity on these issues so sponsors can prepare for the transition date, which is now only 18 months away.

IV. PhRMA Offers Several Recommendations for Enhancement of the Purple Book (Question 2).

PhRMA appreciates FDA's plan to develop an improved Purple Book that will include "more information about approved biological products" and "provide a modernized, interactive user experience."[55] We offer three recommendations for FDA's consideration in this process.

First, PhRMA appreciates that the Biosimilars Action Plan lists as a key action "[e]nhancing the Purple Book to include . . . *information relating to reference product exclusivity determinations*."[56] PhRMA agrees that this is a key action. We further urge FDA to state in the Purple Book the Agency's commitment to publish prompt reference product exclusivity decisions at the time of biologic approval.[57] Prompt publication of this information is essential to provide certainty and transparency to all stakeholders. Specifically, prompt exclusivity decisions allow reference product sponsors the ability to understand much earlier whether their products will be entitled to exclusivity, and prompt publication of those decisions allows potential biosimilar developers to know whether exclusivity will affect the timing of biosimilar application submission and approval. We also recommend that the Purple Book include information about orphan-drug exclusivity and pediatric exclusivity applicable to the reference product, which is information contained in the Orange Book. All stakeholders would benefit from this information being in one place and would be able to make more informed investment decisions. PhRMA also encourages FDA to include the name of the BLA holder in the Purple Book.

Second, we recommend that the Purple Book state that an interchangeability determination reflects FDA's judgment that an interchangeable biosimilar product "may be substituted for the reference product," not another biosimilar product, and has been demonstrated to meet the statutory interchangeability standard, including with respect to switching and alternating with the reference product.[58] This statement could appear in a

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[54] *Id*. at 19-24.

[55] FDA, *Biosimilars Action Plan: Balancing Innovation and Competition*, at 7 (July 2018) (Biosimilars Action Plan).

[56] *Id*. (emphasis added).

[57] PhRMA, Comments to Docket No. FDA-2013-D-1165, at 16-17 (Oct. 6, 2014). PhRMA also recommends that FDA finalize the draft guidance on reference product exclusivity consistent with our comments. *See id*.

[58] PHSA §§ 351(i)(3) & (k)(4), 42 U.S.C. § 262(i)(3) & (k)(4).

glossary that includes definitions of biosimilarity and interchangeability, among other terms. This content is especially important considering that once multiple interchangeable products have been approved for a single reference product, there is risk that stakeholders will treat them as interchangeable with each other, even though they have only been shown interchangeable with the reference product. This risk is particularly acute given the extensive experience many physicians, patients, and pharmacists have with generic drugs that are substitutable with one another. Individual interchangeable products could have greater differences in structure, container closure system, and other attributes from each other than from the reference product. Moreover, two interchangeable products likely will not have been evaluated to determine if alternating or switching between them induces an immunogenic response.[59] Consequently, not only might multiple interchangeable products not meet the statutory standard of interchangeability with respect to one another,[60] but substitution among them may present the risk of additional or different immunogenicity issues than would result from substitution for the reference product with a particular interchangeable product.[61] It is important for FDA to convey clearly the meaning of an interchangeability determination in the Purple Book to avoid inadvertent substitution of non-interchangeable products and to promote prescriber confidence in interchangeable products.

Finally, adding patent information to the Purple Book as requested by several stakeholders is not possible under current law and would strain FDA resources. Unlike the FDCA,[62] the PHSA provides no statutory basis for requiring submission and publication of patent information for biologics or for not approving a BLA on the ground that it does not include patent information. Further, under the BPCIA, patents do not dictate when FDA may approve a biosimilar application. Although section 351(l) of the PHSA includes patent litigation provisions, FDA has explained that they "are parallel to, but separate from, the FDA review process," with FDA's involvement limited to receiving and publishing notice of certain patent infringement complaints.[63] Implementing a patent listing process for biologics would consume FDA resources even though the BPCIA's patent litigation provisions already provide a mechanism for the reference product sponsor and biosimilar applicant to identify patents for which each party "believes a claim of patent infringement could reasonably be asserted" based on commercial marketing of the biosimilar by an unlicensed person.[64] Further, if prospective biosimilar applicants seek information regarding patents relevant to a potential reference product at an earlier time, they may conduct a patent search and freedom-to-operate analysis

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[59] *See* FDA, Draft Guidance, *Considerations in Determining Interchangeability with a Reference Product*, at 16 (Jan. 2017) (Interchangeability Draft Guidance) ("[W]ith switching, multiple exposures to each product can prime the immune system to recognize subtle differences in structural features between products, and the overall immune response could be increased under these conditions.").

[60] *See*, *e.g.*, PHSA § 351(k)(4)(A)(ii), 42 U.S.C. § 262(k)(4)(A)(ii) (the applicant for an interchangeable biosimilar must be show that its product "can be expected to produce the same clinical result *as the reference product* in any given patient") (emphasis added).

[61] *See* Interchangeability Draft Guidance, at 16.

[62] *See* FDCA §§ 505(b)(1), (d)(6), (j)(7)(A)(iii), 21 U.S.C. §§ 355(b)(1), (d)(6), (j)(7)(A)(iii) (requiring submission of patent information in an NDA and FDA publication of that information in the Orange Book, and providing grounds for FDA denial of an NDA lacking the required patent information).

[63] Letter from Janet Woodcock, M.D., FDA, to Jeffrey Kushan, Sidley Austin LLP, re: Docket No. FDA-2014-P-1771, at 3 & n.13 (Mar. 25, 2015).

[64] PHSA §§ 351(l)(3)(A) & (B), 42 U.S.C. §§ 262(l)(3)(A) & (B); *see also* PHSA § 351(l)(7), 42 U.S.C. § 262(l)(7).

based on the public record.[65] Thus, even if FDA had authority to implement a patent listing process for biologics, any incremental benefit from this approach would be outweighed by the significant FDA resources required to develop and continually administer the listing process.

V. PhRMA Supports Appropriate Expansion of Biosimilar Labeling to Include Previously-Protected Conditions of Use Through a Clear Process (Question 7).

The *Federal Register* notice asks for input regarding a situation where a biosimilar applicant did not initially seek approval of a reference product condition of use due to patent or exclusivity protection, that protection expires, and the applicant subsequently seeks approval for the condition of use.[66]

In such cases, PhRMA supports prompt and appropriate approval of the condition of use for the biosimilar based on clinical data or scientifically justified extrapolation. PhRMA does not object to FDA's review of a condition of use before the protection expires. But as long as the relevant protection remains in effect, FDA should not publicly discuss or disclose its deliberations (e.g., in advisory committee meeting materials or action packages) regarding whether the product is biosimilar to the reference product with respect to the protected condition of use.[67] For example, in the case of an orphan-protected use, diluting the value of orphan-drug exclusivity could undermine incentives to develop biologics for new indications. PhRMA also supports adoption of a clear process that enables the applicant to obtain approval of a previously protected condition of use promptly upon expiry of the protection.

VI. PhRMA Supports Further Elucidation of FDA's Approach to Analytical Similarity (Question 4).

In the *Federal Register* notice, FDA stated that it "recognizes that obtaining and testing multiple lots of the reference product adds to the costs of developing a biosimilar product" and asks for input on what the Agency can do "to help reduce development costs arising from analytical studies of the reference product without compromising FDA's robust scientific standards for licensure of products under section 351(k) of the PHS Act[.]"[68] In particular, FDA requested comments on "(1) the number of lots of each product (the proposed biosimilar product and the reference product) that should be used in analytical studies submitted to support licensure of a proposed biosimilar product; and (2) how a 351(k) applicant should

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[65] Additionally, one speaker at the public hearing suggested that FDA publish in the Purple Book "information concerning the history and timing of manufacturing changes for originator biologics." Statement by Steven Lucio, Pharm.D., Vizient, Inc., Public Hearing Webcast Part 2, at 15:35-16:21 (Sept. 4, 2018), *available at* https://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm610692.htm. We agree with the legal concerns raised by an FDA panelist regarding FDA's ability to disclose this trade secret information under current law, *see* 18 U.S.C. § 1905; 21 C.F.R. § 20.61(c), and believe the proposal would present significant burden but questionable benefit.

[66] 83 Fed. Reg. at 35,156. Patents or exclusivity are not the only reason why a biosimilar product might not be approved for all of the reference product's conditions of use. For example, the biosimilar applicant might not have adequately justified the extrapolation of a demonstration of biosimilarity to a given condition of use or the condition of use might have been approved for the reference product after approval of the biosimilar product.

[67] It therefore might be necessary to redact information from the action package that FDA makes publicly available.

[68] 83 Fed. Reg. at 35,156.

account for and evaluate any observed variability in analytical attributes among lots of the reference product or the proposed biosimilar product."[69]

PhRMA supports FDA's goal of reducing the cost of analytical studies intended to demonstrate biosimilarity. However, PhRMA urges FDA to ensure that there is appropriate sampling and analysis of the reference product. The usage of too few lots of reference product might make it challenging to determine whether the proposed biosimilar product in fact meets the standard for biosimilarity to the reference product. PhRMA asks that FDA take into account the fact that "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" because a biosimilar developer "is likely to have a different manufacturing process . . . from that of the reference product and no direct knowledge of the manufacturing process for the reference product."[70]

We recognize that FDA recently withdrew its draft guidance entitled *Statistical Approaches to Evaluate Analytical Similarity*.[71] We look forward to FDA's publication of revised draft guidance on these issues pursuant to its performance goals under the Biosimilar User Fee Act.

In addition, the Biosimilars Action Plan discusses FDA's plans to "develop information resources and development tools that can assist biosimilar sponsors in developing high quality biosimilar and interchangeable products" including the Agency's plans to "develop an index of critical quality attributes for use in comparing proposed biosimilars to certain reference products."[72] The Agency's rationale for the development of such an index is explained in the Biosimilars Action Plan: "The elucidation of these features can allow sponsors to better understand how the FDA evaluates data from comparative analytical studies performed to support a demonstration of biosimilarity."[73] Critical quality attributes (CQAs) are used to gain an understanding of a product and the manufacturing processes used to make that product, and information on a given product's CQAs may contain proprietary data such as unique analytical methods, quality control procedures, or even product specification ranges.[74] PhRMA is concerned by the suggestion that FDA would disclose CQAs for certain innovator biologics and therefore, disclose the innovator manufacturer's trade secret information, and we believe that this proposal raises similar legal concerns to those described in section II. PhRMA urges FDA to

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[69] *Id*.

[70] FDA, Guidance for Industry, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, at 6 (Apr. 2015).

[71] *See* FDA, *FDA Withdraws Draft Guidance for Industry: Statistical Approaches to Evaluate Analytical Similarity* (June 21, 2018), *available at* https://www.fda.gov/Drugs/DrugSafety/ucm611398.htm.

[72] Biosimilars Action Plan, at 6.

[73] *Id*.

[74] The International Council for Harmonisation (ICH) Q8 (R2) guideline defines CQA as a "physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality." While certain attributes will be standard across products (e.g., bioburden), additional CQAs, including the analytical method(s) used to evaluate a CQA, will be unique to individual products based on a product's specific risk profile. Therefore, disclosing CQAs for certain reference products is likely to constitute disclosure of trade secrets.

carefully consider the legal issues associated with the development of a CQA index and related disclosure of trade secrets.

Instead of creating a CQA index, PhRMA encourages the Agency to foster innovation in biologics product development by taking a more risk-based approach to the evaluation of CQAs and associated product specifications to ensure that product specifications are clinically relevant (i.e., have a well-characterized impact on safety and effectiveness of the product) and not unnecessarily restrictive. Unnecessarily tight specifications can lead to batch failures, which in turn could even contribute to drug shortages to the detriment of patients. In addition, unnecessarily restrictive specifications can inhibit or deter pursuit of continual product and process improvements, also to the detriment of patients. PhRMA encourages FDA to explore risk-based approaches for clinically relevant specifications, including by providing guidance on how and when modeling and prior knowledge can contribute to specification development.

VII. PhRMA Supports the Appropriate Use of State-of-the-Art Tools in Development of All Biological Products (Goal 1).

FDA also requested input on how the Agency can "[f]acilitate the efficient development of biosimilar and interchangeable products using state-of-the-art science."[75] The Biosimilars Action Plan states that "FDA's goals in this area . . . include . . . *in silico* modeling and simulation to evaluate pharmacokinetic and pharmacodynamic response versus clinical response relationships using existing clinical data," with a goal of "allow[ing] development programs to be more efficient and . . . reduce the size of clinical studies."[76] PhRMA supports the use of state-of-the-art methods to facilitate greater efficiency in developing both innovative and biosimilar products.[77] However, PhRMA suggests that the Agency acknowledge the limitations that exist within the current state of science. In particular, PhRMA believes that methods such as *in silico* modeling and simulation do not currently have the ability to reliably predict safety, efficacy, or immunogenicity and therefore would not provide appropriate evidence to support a showing of biosimilarity or be predictive of immunogenicity without supportive clinical data. Specifically, immunogenicity responses are difficult to predict and may depend on a number of factors, including process-related factors that may be different for every molecule. Therefore, PhRMA believes that the use of clinical studies to assess biosimilarity and in particular to evaluate immunogenicity are necessary until such modeling and simulation methodologies are further advanced.

VIII. FDA Should Continue to Approve Reference Product BLAs and Supplemental BLAs That Meet Statutory Licensure Requirements (Question 6).

FDA requested input on what the Agency can do "to ensure that product changes during the lifecycle of reference product (e.g., changes in product presentation) are adequately

[75] 83 Fed. Reg. at 35,156.

[76] Biosimilars Action Plan, at 6.

[77] *See* FDA, PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022, at 30-31.

incentivized without inappropriately deterring competition from biosimilar and interchangeable products, with the overall goal of balancing of innovation and competition[.]"[78]

PhRMA is concerned by a recent statement that FDA intends "to compel the branded drug makers who have biologics on the market to tighten up their manufacturing, to have less variance of their biologics that are currently on the market . . . to make it easier to copy those drugs in smaller studies."[79] PhRMA supports manufacturers' adoption of post-approval manufacturing changes in the interest of innovation and public health. The described approach would discourage reference product manufacturers from making process improvements or other changes that are necessary, for example, to ensure an adequate supply of the product (e.g., when a raw material for the biological product is discontinued) and could add substantial costs to continued manufacturing of a biological product. It also seemingly would preclude product improvements that could benefit patients. PhRMA therefore recommends that FDA instead preserve innovators' ability to make these changes, consistent with the PHSA,[80] increase innovators' flexibility by adopting more risk-based approaches to the evaluation of post-approval changes, and focus on other mechanisms to facilitate biosimilar development. To that end, PhRMA also urges FDA to align its planned Draft Guidance on "Processes and further considerations related to post-approval manufacturing changes for biosimilar biological products"[81] with its draft guidance entitled "Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products."[82] PhRMA believes that the guidances should be combined and that any Agency guidance on post-approval changes for biologic products should consistently apply the same concepts and risk-based approaches across both innovator biologics and biosimilars.[83]

IX. PhRMA Supports Appropriate FDA Efforts to Address Access to Reference Product Samples (Goal 6).

FDA asked for input on how FDA can "[s]upport market competition by addressing attempts to game FDA requirements or otherwise delay market entry of competing biological products."[84] One speaker at the public hearing addressed access to reference product samples as related to this goal.

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[78] 83 Fed. Reg. at 35,156.

[79] CNBC, *CNBC Exclusive: CNBC's Meg Tirrell Interviews FDA Commissioner Scott Gottlieb from CNBC's Healthy Returns Conference Today* (Mar. 28, 2018), *available at* https://www.cnbc.com/2018/03/28/cnbc-exclusive-cnbcs-meg-tirrell-interviews-fda-commissioner-scott-gottlieb-from-cnbcs-healthy-returns-conference-today.html.

[80] *See* PHSA § 351(a)(2)(C), 42 U.S.C. § 262(a)(2)(C) (providing that FDA "shall approve" a BLA where the applicant has demonstrated that the proposed product is safe, pure, and potent; the facility meets standards designed to assure that the biological product continues to be safe, pure, and potent; and the applicant has consented to a facility inspection).

[81] Biosimilars Action Plan, at 7

[82] 82 Fed. Reg. 60,750 (Dec. 22, 2017).

[83] PhRMA further urges the FDA to consider and incorporate PhRMA's comments submitted to Docket No. FDA-1995-D-0288 on draft guidance "Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products" into the revised draft or final guidance.

[84] 83 Fed. Reg. at 35,156.

The speaker suggested that "FDA should issue a policy confirming that commercially reasonable access to reference products is a condition of approval under . . . the BPCIA."[85] There is no statutory authority for such a requirement, either in the BPCIA or FDCA (including section 505-1). As noted, the PHSA requires FDA to approve a BLA based upon a demonstration that the proposed product is safe, pure, and potent and that the relevant facility complies with current good manufacturing practice, and upon the applicant's consent to a facility inspection.[86] FDA could evaluate whether REMS supporting documents might appropriately include information about how biosimilar developers might obtain product samples, including the information that biosimilar developers might be required to provide FDA, however.

Further, as part of its ongoing REMS authority, FDA can evaluate the impact of one (or more) risk evaluation and mitigation strategies (REMS) with elements to assure safe use (ETASU) on the health care delivery system and also structure or revise REMS to minimize the impact to the system.[87] PhRMA supports FDA exercising that authority to evaluate whether one or more REMS has had an impact on the availability of biosimilars. FDA could then consider whether there are particular steps the Agency might take to revise or modify REMS to allow for sample access while not undermining the patient safety protections the REMS was imposed to provide. For example, depending on the risks the REMS was imposed to mitigate, FDA might require the biosimilar applicant to submit protocols, informed consent documents, and other relevant materials to ensure the safety protections of the REMS were not undermined.

Although PhRMA supports FDA taking appropriate measures within its existing statutory authority to address product sample access issues, legislation may be useful to fully address the issue. We take seriously the concerns raised about REMS being used to delay biosimilar entry. We are actively engaged with policymakers to develop policy solutions that ensure the timely transfer of samples to biosimilar manufacturers without risking patient safety or establishing a tool that creates an incentive for predatory litigation.

X. PhRMA Supports FDA's Evaluation of the Citizen Petition Process Using Accurate Data (Goal 6).

In reference to how FDA can "[s]upport market competition by addressing attempts to game FDA requirements or otherwise delay market entry of competing biological products,"[88] the above-mentioned speaker at the public hearing also addressed issues related to citizen petitions. The speaker asked that FDA "promptly deny citizen petitions that seek to delay or prevent biosimilar approvals."[89] The speaker claimed that academic studies have shown that "citizen petitions are rarely granted, are mostly filed at the end of a product's life cycle, and delay the approval of affordable medicine."[90] The accompanying slide claims that "8% of these

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[85] Statement by Bruce A. Leicher, Momenta Pharmaceuticals, Inc., Public Hearing Webcast Part 2, at 58:10-58:21, 1:04:09-1:04:56 (Sept. 4, 2018), *available at* https://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/ucm610692.htm.

[86] PHSA § 351(a)(2)(C), 42 U.S.C. § 262(a)(2)(C).

[87] FDCA §§ 505-1(f)(5)(B) & (g)(4), 21 U.S.C. §§ 355-1(f)(5)(B) & (g)(4).

[88] 83 Fed. Reg. at 35,156.

[89] Webcast Part 2, 1:02:35 -1:02:42.

[90] *Id*. at 1:02:42-1:03:52.

Citizen Petitions are granted by FDA . . . [s]uggest[ing] they are intended as barriers, not science-based."[91]

PhRMA addressed issues relating to the citizen petition process in our comments submitted in November 2017 on "Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access."[92] With respect to the claim that FDA grants a small percentage of citizen petitions, we noted that the underlying studies relied upon data that count only the raw number of petitions denied—including petitions that FDA denied without comment on their merits due to the Agency's approach to implementing section 505(q) of the FDCA.[93] Neither FDA's data on responses to citizen petitions[94] nor the studies cited to support claims that innovators' petitions generally are frivolous distinguish between these non-substantive denials and denials of citizen petitions on the merits.[95]

Moreover, as noted in PhRMA's Hatch-Waxman comments, it is incorrect to assume that even substantively denied petitions are automatically frivolous. To cite a recent example, in January 2017 FDA denied a citizen petition that requested, among other things, that FDA "convene a Part 15 hearing to obtain public input" on the Agency's implementation of the BPCIA's interchangeability provisions.[96] FDA stated that "at this time, FDA does not intend to hold a public hearing or public meeting concerning the draft guidance" entitled *Considerations in Demonstrating Interchangeability with a Reference Product* because "[t]he Agency does not believe that such a hearing is necessary given the other mechanisms at stakeholders' disposal to interact with FDA on this issue."[97] In July 2018, however, FDA announced the public hearing on "Facilitating Competition and Innovation in the Biological Products Marketplace" that, as

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[91] *Id*.

[92] *See* PhRMA, Comments to Docket No. FDA-2017-N-3615, at 5-11 (Nov. 17, 2017) (PhRMA Hatch-Waxman Comments).

[93] *Id*. at 6. FDA explains its policy of denying section 505(q) petitions on non-substantive grounds as follows:

> [W]e do not interpret section 505(q) to require a substantive final Agency decision within 150 days on the approvability of a specific aspect of a pending application when a final decision on the approvability of the application as a whole has not yet been made and when to render such a decision could deprive an applicant of procedural rights established by statute and regulations. In such a situation, we would expect to deny a petition without comment on the substantive approval issue.

FDA, Guidance for Industry, *Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act*, at 14 (Rev. 1, Nov. 2014).

[94] *See, e.g.*, FDA, *Ninth Annual Report on Delays in Approvals of Applications Related to Citizen Petitions and Petitions for Stay of Agency Action for Fiscal Year 2016*, at 6 (Jan. 2018) (noting that the category for "denied" petitions "includes instances where FDA issued a denial without comment on the substance of one or more of the requests").

[95] *See* PhRMA Hatch-Waxman Comments, at 7 n.27.

[96] Letter from Janet Woodcock, M.D., FDA, to Perry Siatis, AbbVie Inc., re: Docket No. FDA-2015-P-4935, at 3-4 (Jan. 17, 2017); Citizen Petition, Docket No. FDA-2015-P-4935, at 20 (Dec. 16, 2015).

[97] *Id*.

requested by the petition, addressed issues relating to interchangeability.[98] It therefore would be incorrect to infer from FDA's denial of the citizen petition that the petition lacked merit.

XI. PhRMA Supports FDA's Continued Efforts to Educate Stakeholders About Biosimilars (Question 3).

FDA asked for input on what the Agency can do "to ensure that confidence in [biosimilar and interchangeable] products among patients, healthcare providers, pharmacists, and other stakeholders will continue to grow[.]"[99]

One element of the Biosimilars Action Plan is "[d]eveloping effective communications to improve understanding of biosimilars among patients, clinicians, and payors."[100] PhRMA strongly supports FDA's continued efforts, including those described in the Biosimilars Action Plan, to raise awareness of the Agency's role in the biosimilar approval process, increasing the public's understanding of both biologics and biosimilars, and helping stakeholders understand the data and information that goes into biosimilarity determinations. Confidence among stakeholders is essential to develop the market for biosimilar products.

[98] 83 Fed. Reg. at 35,156.

[99] *Id.*

[100] Biosimilars Action Plan, at 8.

XII. Conclusion

PhRMA appreciates FDA's consideration of these comments and the opportunity to speak at the public hearing. We look forward to a continued dialogue with the Agency and other stakeholders on these issues.

Respectfully submitted,

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/s/
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