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Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

CITIZEN PETITION

Pfizer Inc. (“Pfizer”) submits this petition pursuant to 21 C.F.R. § 10.30 to ask the Commissioner of Food and Drugs to issue guidance clarifying appropriate sponsor communications about the nature and properties of biosimilar products.

I. ACTIONS REQUESTED

We request that the Food and Drug Administration (“FDA” or “Agency”) issue guidance to ensure truthful and non-misleading communications by sponsors concerning the safety and effectiveness of biosimilars, including interchangeable biologics, relative to reference product(s). The specific actions requested are described in detail below.

II. STATEMENT OF GROUNDS

A. Pfizer’s Commitment to Biosimilar Product Development

Pfizer markets biologics licensed under section 351(a)¹ of the Public Health Service Act (“PHS Act”) as well as biosimilars licensed under section 351(k)² of the PHS Act and believes that both are important treatment options for patients. Just as there is a need for policies that support innovation, there is also a need for policies that ensure that patients and physicians have truthful and non-misleading information that encourages appropriate uptake of biosimilars so that biosimilars can reach their full potential for patients.

Biosimilar medicines are a critically important aspect of the future of patient treatment, and Pfizer is committed to making the full potential of biosimilar medicines a reality across the communities we serve. For thirty years, Pfizer has dedicated significant resources to providing high-quality biologic medicines, with a development program supported by robust clinical and analytical data. Pfizer continues building on this record through the development of biosimilars, leveraging ten years of experience with biosimilars outside the U.S. Pfizer is proud of the FDA’s recent approval of RETACRIT[®] (epoetin alfa-epbx), a biosimilar to EPOGEN[®] and PROCRI[®]

¹ 42 U.S.C. § 262(a).

² 42 U.S.C. § 262(k).

(epoetin alfa) for all indications of the reference products, as well as the Agency’s approval of NIVESTYM™ (filgrastim-aafi), a biosimilar to NEUPOGEN® (filgrastim) for all eligible indications of the reference product. RETACRIT is the first and only biosimilar erythropoiesis-stimulating agent to be approved in the U.S. Pfizer is also the commercial partner to Celltrion Healthcare with respect to the biosimilar INFLECTRA® (infliximab-dyyb). We are highly supportive of biosimilar development, and we continue to develop a robust pipeline of additional biosimilar products.

B. FDA’s Efforts to Foster Biosimilar Development and Adoption

Congress, through the enactment of the Biologics Price Competition and Innovation Act of 2009 (“BPCIA”), established an abbreviated pathway for the licensure of biosimilars, including interchangeable biologic products. In enacting the BPCIA, Congress intended to help reduce healthcare costs by enhancing patient access to additional biological treatment options. FDA has engaged in various initiatives aimed at encouraging and facilitating the development and approval of biosimilars, as evidenced by the numerous biosimilar-related guidance documents FDA has issued, the Agency’s development and distribution of educational materials through its October 2017 Biosimilars Education Campaign, the Agency’s Biosimilar User Fee Act performance goals, and the newly released Biosimilars Action Plan.³ Despite these continued efforts, significant biosimilar cost savings have yet to be realized due to slower than expected development, approval, acceptance, and availability of biosimilars in the U.S. market. It took five years after the enactment of the BPCIA before the first biosimilar product was able to obtain approval in the U.S., and since then only eleven additional biosimilar products have received marketing approval, with the majority obtaining approval within the past year. For the few biosimilars that have both obtained marketing approval and achieved commercial launch, market acceptance, in general, has been much slower than anticipated. We believe that a major factor contributing to this slow uptake is a lack of market confidence in biosimilars resulting from the efforts of certain reference product sponsors to disseminate false and misleading information that casts doubt about the safety and efficacy of biosimilars in the minds of patients and prescribers.

In contrast, the European Union (“EU”), which implemented a regulatory pathway for the approval of biosimilars five years prior to the U.S., is seeing far greater market acceptance of biosimilars. For example, in a recent survey conducted by the Decision Research Group, six months following the launch of rituximab biosimilars, the majority of surveyed oncologists in Germany responded that they prescribed at least one of the rituximab biosimilars to their patients and were satisfied with their use.⁴ Similarly, when asked about the adoption of trastuzumab biosimilars, surveyed European oncologists reported that they anticipate prescribing the biosimilars to the majority of patients eligible for intravenous trastuzumab therapy.⁵

³ Biosimilars Action Plan: Balancing Innovation and Competition, *available at* <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm613761.pdf>, accessed July 18, 2018.

⁴ Aided, H. The European Biosimilars Landscape: What to Expect in the Year Ahead. (April 10, 2018), *available at* <https://www.biosimilardevelopment.com/doc/the-european-biosimilars-landscape-what-to-expect-in-the-year-ahead-0001>.

⁵ *Id.*

Furthermore, although there is variability in the EU in the penetration of biosimilars by country and therapeutic area, an analysis by QuintilesIMS (now IQVIA) found that, across therapeutic areas, the competition provided by biosimilars has contributed to increased patient access.⁶ This increased patient access extends not only to biosimilars, but also to their reference products and other products in the same therapeutic class.⁷

A number of factors are thought to have contributed to the robust uptake of biosimilars in the EU, including payers employing tools intended to incentivize the adoption of biosimilars and health authorities issuing guidelines promoting switching of patients to biosimilars.⁸ We believe that in the U.S., on the other hand, payer reimbursement policies are in fact impeding adoption of biosimilars. While we understand that biosimilar reimbursement policies are not directly within the purview of FDA, dissemination of false or misleading information about the safety or efficacy of biosimilars, whether to patients and prescribers or directly to payers, has the potential to affect payer decisions about biosimilar reimbursement, as well as patient and healthcare professional confidence in biosimilars. Consequently, we believe that the actions that FDA takes to encourage the uptake of biosimilars in the U.S., including any steps aimed at ensuring that information reference product sponsors disseminate about biosimilars is truthful and non-misleading, have the potential to help shape payers' views in support of biosimilar access.

Given this experience to date, we are pleased that FDA has focused on encouraging biosimilar competition, consistent with the Trump Administration's May 2018 *Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs*, which states that FDA will issue policies to improve "the availability, competitiveness, and adoption of biosimilars as affordable alternatives to branded biologics" and will continue its educational efforts directed at clinicians, patients, and payers about biosimilar and interchangeable products.⁹ Consistent with that approach, on March 7, 2018, FDA Commissioner Scott Gottlieb addressed the importance of encouraging the development and use of biosimilars in a speech to the America's Health Insurance Plans' ("AHIP") National Health Policy Conference.¹⁰ Dr. Gottlieb stated, in pertinent part:

"FDA is invested in making sure that the new biosimilar pathway works, and that we can help **facilitate a robust market for these products**. So, we take note when we see **market practices** that can **reduce** the incentive for sponsors to invest in the **development of biosimilars** in the first place." (emphasis added)

⁶ QuintilesIMS, The Impact of Biosimilar Competition in Europe (May 2017), available at https://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017_V9.pdf.

⁷ *Id.*

⁸ See Rademacher K. and Edger T. The Influence of Europe on the Pricing, Update, and Overall Impact of Biosimilars. *Journal of Clinical Pathways*. 2017;3(19): 47-50; available at <https://www.journalofclinicalpathways.com/article/influence-europe-pricing-uptake-and-overall-impact-biosimilars>

⁹ Department of Health & Human Services, American Patients First: The Trump Administration Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs, (May 2018), available at <https://www.hhs.gov/sites/default/files/AmericanPatientsFirst.pdf>.

¹⁰ Capturing the Benefits of Competition for Patients, *available at* <https://www.fda.gov/NewsEvents/Speeches/ucm599833.htm>, accessed July 11, 2018.

With respect to encouraging the use of biosimilars, Dr. Gottlieb further stated:

“Physician and patient confidence in the quality and safety of biosimilar products is critical to their market acceptance. And at FDA, we want to address any misconceptions or concerns that may be out there.” (emphasis added)

On July 18, 2018, Dr. Gottlieb, during a speech¹¹ at the Brookings Institution, discussed the need for maintaining balance between biosimilars innovation and competition when announcing the release of FDA’s Biosimilars Action Plan. Dr. Gottlieb stated, in pertinent part:

“The branded drug industry didn’t build its success by being business naïve. They are smart competitors. But that doesn’t mean we need to embrace all of these business tactics, or agree that they’re appropriate.”

“Sometimes it feels as if we’re seeing the biosimilars version of ‘Groundhog Day,’ with brand drug makers replaying many of the same tactics, and all of us being too susceptible to **many of the same misconceptions** about **biosimilars’ safety and efficacy** relative to originator biologics.” (emphasis added)

Pfizer agrees with Commissioner Gottlieb’s statements regarding the inappropriate tactics of some reference product sponsors to fuel misconceptions concerning the safety and efficacy of biosimilars, relative to originator biologics, in an effort (as was the case in the early generic marketplace) to raise doubts among prescribers in prescribing, and reduce patient confidence in being treated with biosimilars. While biosimilars are relatively new to the market, the concepts associated with fostering successful competition are well-established given our long history of enhancing competition and patient access via generic drugs. However, in contrast to generic drugs, there are fewer targets for biosimilar competition, and the costs and other obstacles associated with bringing a biosimilar to market are generally higher. If the United States does not get this right now, we may never be able to achieve for biosimilars what we have achieved in the drug context with generic competition.

The Biosimilars Action Plan is focused on four key areas:

- (1) Improving the efficiency of the biosimilar, including interchangeable, product development and approval process;
- (2) Maximizing scientific and regulatory clarity for the biosimilar product development community;
- (3) Developing effective communications to improve understanding of biosimilars among patients, clinicians, and payors; and
- (4) Supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay competition.¹²

¹¹ Dynamic Regulation: Key to Maintaining Balance Between Biosimilars Innovation and Competition, *available at* <https://www.fda.gov/NewsEvents/Speeches/ucm613452.htm>, accessed July 18, 2018.

¹² Biosimilars Action Plan: Balancing Innovation and Competition, at 5.

With respect to the third key area, the Biosimilars Action Plan lists certain “priority deliverables.” First, it highlights that FDA released (in October 2017) the Biosimilar Education and Outreach Campaign, updated its Biosimilars website, and mentions that the Agency plans to develop additional educational resources.¹³ Second, it highlights a webinar hosted by FDA in December 2017 that provided an overview of the regulatory framework and the development and approval of biosimilar products in the U.S., and announces the Agency’s intention to host a “second webinar for Continuing Education credit that covers information related to the labeling for and prescribing of biosimilar, [including] interchangeable products,” as well as “additional webinars on topics of interest identified by stakeholders and the FDA.”¹⁴ Third, it highlights a forum FDA held in April 2018 “to further engage stakeholders, address knowledge gaps and encourage stakeholder use of the FDA Biosimilars webpage and resources,” and announces FDA’s plans to “develop a one-pager for patient audiences and pursue video-format communications that can be used on social media for patient and other key audiences.”¹⁵

While these efforts are laudable, we believe it is essential that they include a strong emphasis on the issues addressed in this Petition. As noted, some current communications by reference product sponsors concerning the safety and effectiveness of biosimilars, including interchangeable biologics, relative to reference products undermine efforts to enhance stakeholder confidence in biosimilars by creating doubt and confusion about the safety and effectiveness of these products. This should serve as an impetus for the expeditious issuance of guidance, and associated public education, on communications concerning the safety and effectiveness of biosimilar, including interchangeable, products. Otherwise, the current reluctance to prescribe and use biosimilars will only continue to grow, hurting future development of these products and undermining the Agency’s efforts to foster a robust and competitive market.

C. Statutory and Regulatory Background

Pursuant to section 351(a) of the PHS Act and implementing regulations, approval of a biologics license application (“BLA”) constitutes a determination by FDA that the product and the establishment(s) used for the manufacture of the product meet applicable requirements to ensure the continued “safety, purity, and potency of such products.”¹⁶ Biologics approved under section 351(a) may be “reference” biologic products, which is the term for a biologic referenced in a biosimilar or interchangeable biologic product application and against which a biosimilar product subject to an application under section 351(k) is evaluated.¹⁷

As amended by the BPCIA, section 351(k) of the PHS Act sets forth the requirements for a proposed biosimilar, including an interchangeable biologic product.¹⁸ An application for a biologic product submitted under section 351(k) must include information to demonstrate that (1) the biologic is biosimilar to the reference product; (2) the biologic and the reference product

¹³ *Id.* at 8.

¹⁴ *Id.*

¹⁵ *Id.*

¹⁶ 21 C.F.R. § 601.2(d).

¹⁷ 42 U.S.C. § 262(i)(4).

¹⁸ 42 U.S.C. § 262(k).

utilize the same mechanism(s) of action for the condition(s) of use prescribed, recommended, or suggested in the proposed labeling to the extent that the mechanism(s) are known for the reference product; (3) the condition(s) of use prescribed, recommended, or suggested in the labeling for the biologic have been previously approved for the reference product; (4) the route of administration, dosage form, and strength of the biologic are the same as the reference product; and (5) the “facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent.”¹⁹

A biosimilar licensed under section 351(k) is “highly similar to the reference product notwithstanding minor differences in clinically inactive components” and has “no clinically meaningful differences” from the reference product in terms of safety, purity, and potency.²⁰ A product deemed by FDA to be an interchangeable biologic is a biosimilar that has met additional statutory criteria for product evaluation and testing and that may be substituted for the reference product at the pharmacy level without involvement of the prescriber. Specifically, an interchangeable biologic must meet the standards set forth in section 351(k)(4):

[T]he biologic (1) is biosimilar to the reference product and (2) can be expected to produce the same clinical result as the reference product in any given patient and (3) 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.²¹

To date, FDA has not approved any interchangeable biologics.²²

Biologic products marketed pursuant to BLAs meet the definition of a “drug” under the FD&C Act and are subject to certain of the Act’s drug provisions, including the misbranding prohibition. Thus, as with communications for drugs, certain communications may misbrand biologic products if they are false or misleading. Section 502 of the FD&C Act states that a drug shall be misbranded if its “labeling is false or misleading in any particular”²³; therefore, communications by reference product sponsors that represent or suggest that biosimilars, including interchangeable biologics, are or may not be safe or effective misbrand the reference product under the FD&C Act.²⁴ Additionally, a promotional communication that makes an unsubstantiated comparison representing or suggesting that a drug is safer or more effective than

¹⁹ 42 U.S.C. § 262(k)(2)(A)(i).

²⁰ 42 U.S.C. § 262(i)(2).

²¹ 42 U.S.C. § 262(k)(4).

²² CDER - List of Licensed Biological Products, *available at* <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM560162.pdf>, updated June 6, 2018; CBER - List of Licensed Biological Products, *available at* <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM560162.pdf>, updated July 2, 2018.

²³ 21 U.S.C. § 352(a); 21 C.F.R. § 201.6(a).

²⁴ 21 U.S.C. § 352(a).

another drug is considered false or misleading.²⁵ Thus, communications by a reference product sponsor that imply that its reference product is more effective or safer than the biosimilar are false and misleading, especially given the statute framework²⁶ specifies that a biosimilar is highly similar to and has no clinically meaningful differences from the reference product. Any such false and misleading statements would misbrand the reference product and cause its distribution to be prohibited under the FD&C Act.²⁷

D. The Need for Clearly Defined Guidance

1. False and Misleading Representations About Reference Products and Biosimilars

As noted, the introduction of biosimilars in the U.S. was intended to increase competition by providing additional safe and effective biologic treatment options, thereby reducing healthcare costs. This intent will be thwarted if reference product sponsors provide patients and healthcare professionals with incomplete or misleading information in promotional materials. Unfortunately, Pfizer has observed some reference product sponsor-created physician- and patient-directed materials that mischaracterize important elements of the biosimilar criteria and create doubt and confusion about the safety and efficacy of biosimilars.

Despite the fact that the PHS Act specifies that a biosimilar is “highly similar to and has no clinically meaningful differences” from the reference product,²⁸ certain patient-directed materials and social media disseminated by reference product sponsors omit or misstate key aspects of the definition of a biosimilar. For example, the textual summary comparing biosimilars and generics on Genentech’s “Examine Biosimilars” website explains that “FDA requires a biosimilar to be highly similar, but not identical to the [reference product]”, but fails to state that an approved biosimilar must have no clinically meaningful differences from the reference product.²⁹ A recent tweet by Amgen Biosimilars also contravenes the statutory standard that a biosimilar is highly similar to and has no clinically meaningful differences from the reference product: “Biologics or biosimilars? It’s not just apples to apples. While #biosimilars may be highly similar to their #biologic reference products, there’s still a chance that patients may react differently. See what you’re missing without the suffix: <http://bit.ly/2G2zGTa>.”³⁰

²⁵ See 21 C.F.R. § 202.1(e)(6)(ii).

²⁶ 21 U.S.C. § 262(i)(2)-(3).

²⁷ See 21 U.S.C. §§ 352(a), 352(n), and 331(a); 21 C.F.R. § 202.1.

²⁸ 42 U.S.C. § 262(i)(2).

²⁹ Genentech, Examine Biosimilars - Biosimilars vs. Generics, *available at* <https://www.examinebiosimilars.com/biosimilars-vs-generics.html>, accessed June 12, 2018. The video posted on the website eventually explains at 1:04 that a biosimilar is “[a] biological product that is *highly similar* to its reference product – notwithstanding minor differences in clinically inactive components” and “biosimilars cannot have any clinically meaningful differences in: safety, purity, and potency.” *Id.* Conveying this information one-third of the way through the video, but not in the lead or takeaways paragraphs on the website is arguably misleading.

³⁰ Amgen Biosimilars, Apr. 13, 2018 at 5:03 PM, *available at* <https://twitter.com/AmgenBiosim/status/984884845686992896>, accessed June 12, 2018.

Likewise, in a patient brochure entitled, “Finely Tuned – Your Treatment, Your Choice”, Janssen Biotech Inc., maker of REMICADE[®] (infliximab), fails to mention that an approved biosimilar has no clinically meaningful differences from the reference product.³¹ Janssen’s materials also caution, “you may be asked to switch to a biosimilar that works *in a similar way* to REMICADE.”³² The BPCIA explicitly states that a biosimilar is highly similar to the reference product but has the same mechanism of action, meaning that a biosimilar works in the same way as the reference product. Janssen’s materials confuse this distinction by stating that infliximab biosimilars work in a “similar” way to REMICADE.

Reference product sponsors have also mischaracterized the concepts of interchangeability and switching to sow doubt and confusion about biosimilars. For example, the Finely Tuned Brochure states: “[t]he infliximab biosimilar is not approved as interchangeable with REMICADE” and “switching or alternating back and forth between the interchangeable biologic and REMICADE[®] would not cause any changes in safety or how well the treatment works – no infliximab biosimilar has yet proven this.”³³ While INFLECTRA is not designated as interchangeable, it has, in fact, demonstrated that a single switch does not result in different safety or efficacy.³⁴ By emphasizing that the INFLECTRA product is not interchangeable, the manufacturer is clearly attempting to mislead patients into believing that they cannot safely be switched from REMICADE to INFLECTRA by their physician, and that a non-interchangeable product will not have the same results, neither of which is true.

Amgen includes similar messaging in a YouTube video intended to explain the importance of naming conventions and identifiers for biosimilars, stating, “. . . a switch. This carries risks, given that no two biologic medicines are identical, and thus can behave differently in the body. Switching drugs is not a good idea if your medicine is working for you.”³⁵ Although this statement was made in the broader context of avoiding an inadvertent switch at the pharmacy-level from a reference product to a biosimilar, the implication is that switching generally is risky. Collectively, these materials and statements suggest to patients that using a

³¹ Janssen Biotech, Inc., Finely Tuned Patient Brochure, Dec. 2017, available at http://images.inform.janssen.com/Web/JanssenNAProd/%7B373a365e-a6e8-4d85-91c1-4968bc1f1f63%7D_064590-161214_772213_BIO_FinelyTuned_v2_interactive.pdf (hereinafter, “Finely Tuned Brochure”).

³² *Id.* at 6 (emphasis added).

³³ *Id.* at 5.

³⁴ Switching of patients from REMICADE to INFLECTRA is supported by the results of the NOR-SWITCH study, which is an independent double-blind, randomized clinical trial sponsored by the Norwegian Government. Goll GL, et al., Biosimilar Infliximab (CT-P13) Is Not Inferior to Originator Infliximab: Results from a 52-Week Randomized Switch Trial in Norway [abstract], 2016 American College of Rheumatology/Association of Rheumatology Health Professionals Annual Meeting; Nov. 11-16, 2016; Washington, DC, Abstract #19L. (While we acknowledge that this switch study was conducted vis-à-vis EU-approved REMICADE, Celltrion as part of the INFLECTRA BLA submitted analytical and clinical comparative data and data that provided scientific justification for the relevance of using comparative data against EU-approved REMICADE for a demonstration of biosimilarity to U.S.-licensed REMICADE. FDA accepted this justification stating in the INFLECTRA Summary Review for Regulatory Action: “Therefore, given the lack of safety concerns with transitioning patients from the EU-approved Remicade to CT-P13, safety concerns with transitioning patients from US-licensed Remicade to CT-P13 would not be anticipated, in light of the analytical and PK bridge between EU-approved Remicade and US-licensed Remicade Celltrion, Inc.”)

³⁵ Amgen, The Arrival of Biosimilars - What’s in a name, 2:30-3:08, available at <https://www.youtube.com/watch?v=EHDG2NT3KGg&feature=youtu.be>, accessed June 12, 2018.

non-interchangeable biosimilar or being switched by their physician from a reference product to a biosimilar could lead to a different and potentially unsafe overall result when compared to using the reference product. This directly undermines the BPCIA and FDA’s efforts to promote the use of biosimilars as a means of providing better access to important therapies.³⁶

Misleading statements like these, and the net impression conveyed by such materials, create undue confusion as to biosimilarity and interchangeability, inflate the risks associated with a physician-directed switch to a biosimilar, and cast doubt on the safety and efficacy of biosimilars generally, contrary to the basic intent of the biosimilar regulatory framework and FDA’s efforts, as highlighted by Commissioner Gottlieb, to correct such misconceptions. Guidance that advises on how to properly characterize the relationship between reference products and biosimilars, including interchangeable biologics, is essential to addressing this problem.

2. Truthful and Non-Misleading Communications by Biosimilar Product Sponsors

Also critical to prescriber and patient acceptance of biosimilars is the ability of biosimilar sponsors to disseminate information about the clinical and other data used to support approval of a biosimilar. Indeed, provided biosimilar sponsors communicate such data in a truthful and non-misleading manner -- including ensuring that the presentation of the data does not undermine the “highly similar” and “no clinically meaningful differences” standards -- doing so is lawful and consistent with the First Amendment and FDA policy. Truthful and non-misleading communications about safety and efficacy data relating to a biosimilar’s labeled indication(s) can be wholly consistent with FDA’s recently finalized *Medical Product Communications That Are Consistent With the FDA-Required Labeling — Questions and Answers* (“*Consistent With the FDA-Required Labeling*”) guidance.³⁷ It is also clearly lawful and appropriate for biosimilar sponsors to communicate truthful and non-misleading safety and efficacy data from studies other than ones used to obtain approval of a biosimilar, if the data is presented in a manner that is otherwise consistent with approved labeling. In fact, in certain instances the communication of such data may be necessary to counter misleading information disseminated by reference product sponsors about the safety or efficacy of a biosimilar product relative to its reference product. Thus, the FDA guidance requested herein could also serve to further support biosimilar product sponsors’ efforts to convey such data in a manner that comports with FDA’s *Consistent With the FDA-Required Labeling* guidance.

³⁶ “Biosimilars will provide access to important therapies for patients who need them, . . . Patients and the health care community can be confident that biosimilar products approved by the FDA meet the agency’s rigorous safety, efficacy and quality standards.” FDA News Release: FDA Approves First Biosimilar Product Zarxio, Mar. 6, 2015, available at <https://wayback.archive-it.org/7993/20170111224313/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm>.

³⁷ FDA, *Guidance for Industry: Medical Product Communications That Are Consistent with the FDA-Required Labeling -- Questions and Answers* (June 2018), available at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm537130.pdf>.

E. Requested Actions

We request that FDA issue guidance setting forth the types of sponsor communications about reference products and biosimilars, including interchangeable biologics, that would be inappropriate because they would be false or misleading as further detailed below. FDA in the guidance should also provide examples of communications about biosimilars, including interchangeable biologics, that would not be considered false or misleading, as also detailed below.

- Examples of inappropriate communications that FDA should address in the guidance include misleading representations and suggestions by reference product sponsors that biosimilar products are not as safe or as effective as their corresponding reference biologic products. Because the licensure of a biosimilar product is predicated on a determination that there are no clinically meaningful differences between the biosimilar and its reference biologic in terms of safety, efficacy, or purity,³⁸ any promotional statements by a sponsor that directly or implicitly communicate that biosimilar products are not as clinically safe or effective as the corresponding reference product are false and misleading, and therefore in violation of the FD&C Act and FDA regulations.³⁹ By way of example, FDA should explain that if a reference product sponsor elects to make representations that a biosimilar is “highly similar” to but not “identical” to its reference product, then to avoid giving the false impression that the biosimilar is therefore not as safe or effective as the reference product, the reference product sponsor should also prominently disclose in the same communication that there are no clinically meaningful differences between the biosimilar and the reference product.
- The guidance should also address reference product sponsor communications comparing reference biologics to biosimilars, including interchangeables, that would and would not be considered misleading. The Agency should specify, for example, that reference product sponsor representations or suggestions that biosimilar products are inferior to interchangeable biologics in terms of quality or similarity to the reference product would be misleading and therefore in violation of the FD&C Act. An interchangeable biologic is a biosimilar for which additional data and information required by the BPCIA to meet the interchangeability standard has been provided to FDA. As such, promotional statements by a reference product sponsor that directly or implicitly communicate that biosimilar products differ from interchangeable products in any regard beyond the additional data required to permit substitution without physician intervention at the pharmacy level are plainly misleading.
- By way of another example, the guidance should describe the types of false and misleading claims from reference product sponsors about biosimilars and interchangeability that sow confusion and mistrust among patients and physicians. These statements include misleading suggestions that patients should not be switched by a physician to a biosimilar product without a showing of interchangeability, or that biosimilar products are limited to use in treatment-naïve patients. Neither the BPCIA nor any other provision of law suggests or requires that a biosimilar meet the statutory definition of interchangeability as a prerequisite

³⁸ 42 U.S.C. § 262(i)(2)(B).

³⁹ See, e.g., 21 U.S.C. §§ 352(a), 352(n); 21 C.F.R. § 202.1.

for a physician-directed switch, as compared to a switch performed at the pharmacy-level.⁴⁰ Thus, the guidance should make clear that any communication by a reference product sponsor that suggests that biosimilar products cannot be prescribed to both treatment-naïve and treatment-experienced patients is misleading and therefore inappropriate. Additionally, the guidance should convey that biosimilar product sponsors may present truthful and non-misleading claims based on data from switch studies, provided that such claims do not imply an FDA finding of interchangeability when no such determination has been made.

- In addition, more generally the guidance should clarify that a biosimilar product sponsor may discuss clinical and other data on a biosimilar product, whether or not included in the biosimilar's labeling, with physicians and in promotional materials. FDA's *Guidance for Industry, Labeling for Biosimilar Products*, states, "[b]ecause clinical studies conducted to support a demonstration of biosimilarity generally are not designed to support an independent demonstration of safety or effectiveness, such studies may be misinterpreted in the context of drug labeling, resulting in an inaccurate understanding of the risk-benefit profile of the biosimilar product."⁴¹ However, this statement was made solely in the context of whether such data should be included in biosimilar labeling. Moreover, FDA in the guidance does acknowledge that information and data from a clinical study of a proposed biosimilar product should be described in its labeling "when necessary to inform safe and effective use by a health care provider."⁴² It is essential, however, that FDA make clear that even where clinical data for a biosimilar product are not included in the product's labeling, proactive communication of such information is wholly lawful and appropriate if presented in a truthful and non-misleading manner. Such data may be consistent with the FDA-approved labeling for the product, and the ability of a biosimilar product sponsor to discuss clinical data with physicians and in promotional materials is key to educating physicians and combatting "scare tactics" from certain reference product sponsors.

Issuing a guidance document that addresses the areas identified above will help to ensure that communications concerning the safety and effectiveness of biosimilars, including interchangeable biologics, do not inhibit the use of and reliance on biosimilars for therapeutic treatment, consistent with Commissioner Gottlieb's efforts to facilitate a robust and competitive market for these products.

F. Conclusion

Biosimilars are a key component of the current and future treatment of patients in the U.S., but the uptake of biosimilars has lagged expectations. This is due, in significant part, to the false or misleading statements reference product sponsors are making with respect to the safety and effectiveness of biosimilars, including interchangeable biologics, relative to the reference product(s). Issuing guidance on communications about these products would be an important

⁴⁰ While an interchangeability finding is a prerequisite for substitution at the *pharmacy* level based on certain state laws, pharmacy substitution is a concept that is separate from a *physician-directed* "switch" from one product to another, which constitutes the practice of medicine.

⁴¹ FDA, *Guidance for Industry: Labeling for Biosimilar Products*, July 2018 at 3, available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf>.

⁴² *Id.*

contribution toward eliminating unnecessary barriers to successful market success for biosimilars, including, in the future, interchangeable biologics. Additionally, such guidance is critical to ensuring a fair and level playing field for competition in the interests of patients and our healthcare system. Truthful and non-misleading communications about the safety and efficacy of biosimilars are important to increasing uptake of biosimilars, and securing patient and healthcare provider acceptance.

Pfizer appreciates FDA's efforts to educate patients and providers about biosimilars, and we look forward to FDA's continued initiatives under the newly released Biosimilars Action Plan. For the foregoing reasons, we respectfully request that the Agency issue a guidance incorporating and addressing the areas identified in section II.E. above as part of that critical Action Plan.

III. OTHER REQUIRED INFORMATION

A. Environmental Impact

Under 21 C.F.R. § 25.31, this petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

B. Economic Impact

According to 21 C.F.R. § 10.30, economic impact information will be provided if requested by the Commissioner following review of this petition.

C. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information, known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,



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