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By Electronic Submission

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
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Comments on Facilitating Competition and Innovation in the Biological Products Marketplace, Public Hearing [Docket No. FDA-2018-N-2689]

Dear Madam/Sir:

Pfizer Inc. (Pfizer) is submitting these comments in response to the Federal Register notice of July 25, 2018 (83 FR 35154) on the *Facilitating Competition and Innovation in the Biological Products Marketplace* Public Hearing Request for Comments.

I. GENERAL COMMENTS RELATED TO FEDERAL REGISTER NOTICE CONSIDERATIONS

1. *FDA is aware that many of the biosimilar products that have been licensed by FDA are not yet marketed and available to patients. What can FDA do to help biosimilars and interchangeable products reach patients more quickly after these products are licensed?*

Pfizer Comment

The biosimilars marketplace in the US is at a critical juncture and more needs to be done to ensure success. Opportunities to further advance biosimilars go beyond FDA working alone. These opportunities include:

1. Optimizing development through astute reference product bridging requirements (see Questions 4 and 5), fit for purpose clinical data packages (see Question 9), maximizing review efficiencies (see Question 9), and seamless post-approval processes to add indications (see Question 7).

2. Combating misinformation and instilling confidence in biosimilars through policy development and education. As noted in Question 3, Pfizer appreciates the Biosimilars Education Campaign the Agency initiated in October 2017. FDA should continue and expand upon these educational efforts as the Agency is looked upon as the credible source for education on biosimilars. FDA should elevate its presence at key

platforms/Congresses (e.g., ASCO) and at key influencer institutions. Education alone, however, is not sufficient; it is also essential that FDA take a more active role in combatting misinformation that undermines healthcare provider and patient confidence in biosimilars.

3. Expediting market access by identifying and taking action to address anti-competitive activities and implementing policies to remove barriers and advance uptake; as expanded upon below.

The US government should enforce antitrust laws to prevent reference biologic manufacturers from using exclusionary contracts to create anti-competitive barriers to access for biosimilars.

Exclusionary contracts that foreclose access by patients to biosimilars, anticompetitive product bundling and coercive rebate policies are all designed to perpetuate the use of reference biologics and block insurers from reimbursing and hospitals and clinics from purchasing biosimilars despite their lower pricing.

As a result of these anticompetitive dealings, insurers may be forced to keep biosimilars off the insurance company's medical policy—a published listing of the drugs approved for reimbursement under the insurer's medical benefit — or to designate a biosimilar as reimbursable only in so-called "fail first" cases. In the case of a "fail first" contract, a patient is required to fail on a reference biologic before a biosimilar of that same product will be covered by insurance. Because sound medical practice would not permit a patient to be placed on a biosimilar of the product for which the patient failed to adequately respond, these fail first policies are tantamount to excluding the biosimilar from insurance coverage altogether.

In addition, contracts that require payers to exclude biosimilars from coverage in order to obtain rebates from the reference biologic manufacturers impose substantial financial penalties on insurers. These payers are faced with the ultimate ultimatum: deny insurance coverage of biosimilars or lose what could be tens of millions of dollars annually in rebates. A decision by an insurer to include coverage of the lower cost biosimilar could result in financial penalties in the form of higher costs for all existing patients currently on the reference biologic. Given the cost of biologic drugs generally, contracts that require an explicit commitment to not cover the biosimilar at all or to do so only in the rarest of circumstances substantially limit the market access of the biosimilar.

Even though Medicare and Medicaid permit reimbursement for biosimilars, the existence of these anticompetitive contracts with private insurance company payers substantially impact the overall utilization of biosimilars because healthcare providers, including hospitals and clinics, do not routinely purchase products that lack commercial insurance coverage. As a result, many providers default to prescribing just the reference biologic knowing that it is in stock and covered by virtually all insurers. These engineered coverage restrictions in exclusionary contracts impact provider purchasing behavior and thus magnify exclusion of the biosimilar from the marketplace; we believe that such practices should be prohibited.

The current business model under which pharmacy benefit managers (PBMs) and commercial payers negotiate rebates and discounts from manufacturers as a percentage of list price in exchange for more favorable and often exclusive formulary placement needs to be revised.

The rebate system leads to perverse incentives that drive up list prices, limit competition and in turn, increase consumer out-of-pocket spending. In the commercial insurance marketplaces, the amount of rebates and other fees paid by the manufacturer to the PBM are often based on a percentage of a particular product's list price. As a result, PBMs are incentivized to include on their formularies prescription drug products with high list prices and associated large rebates, as those products will be more profitable to the PBM than drug products with lower list prices (and thus, lower rebates). This profit comes at the expense of consumers. Out-of-pocket costs for consumers who have not met their deductible, or are subject to coinsurance, are calculated based on a percentage of the pharmacy list price, which is not reduced by the substantial drug manufacturer rebates paid to PBMs and health plans. The growth in list prices, and the widening gap between list and net prices, markedly increases consumer out-of-pocket spending, particularly for high-cost drugs.

HHS should shift from rebates towards applying discounts negotiated during upfront pricing.

HHS could consider policy reforms that would move away from rebates (i.e., price concessions not given at the time of sale) and adjust to discounts negotiated during upfront pricing discussions. These upfront discounts should be passed through (in whole or in part) to the plan sponsor, and further passed through to patients at the point-of-sale. As a result of implementing upfront discounts, contractual arrangements between PBMs and health insurance plans would be based on net price (rather than list price), which in turn could potentially increase transparency and improve the competitiveness of biosimilars (by removing the incentive to favor a higher Wholesale Acquisition Cost (WAC) priced product with higher rebates). For example, in today's model, even though the net price could be the same, a product with a $500 WAC and a 30% rebate ($350 net price, $150 rebate) is more attractive to payers because of the opportunity to receive rebate dollars than a competing product with a $400 WAC and a 12.5% rebate (also $350 net price, $50 rebate), and considerably more attractive than a product with a $349 WAC price and no rebate.

HHS should proactively support the use of biosimilars.

There are other approaches that can be implemented that will drive savings with expanded use of biosimilars while preserving physician and patient autonomy in shared decision making:

- **Provide Balanced Incentives**

Biosimilars have been marketed in Europe for 12 years and the experience of the EU with biosimilars can be instructive for the US: to drive uptake of biosimilars, there needs to be a focus on education and balanced incentives for physicians and healthcare providers and the patients they serve. For the latter there needs to be a clear rationale for, and benefit of, increased

biosimilar usage for each stakeholder group. Examples include so-called "gain-share" agreements whereby some savings afforded by biosimilar usage are passed on to healthcare providers (to help fund further areas of healthcare) or reduced co-pay for patients.

There are additional approaches to support the uptake of biosimilars that HHS should consider for implementation. They are:

- **HHS should publicly evaluate and track the uptake of biosimilars under Part B and D, as well as the ASPs of biosimilars compared to their reference products**

  Uptake of biosimilars in the U.S. should play an important role in managing health care costs, and it requires proactive support from multiple stakeholders including HHS, private insurers and employers, as well as patient and physician groups.

- **CMS should ensure immediate coding and coverage of biosimilars following FDA regulatory approval**

  One additional and important incentive utilized in Europe for the US to adopt is the immediate reimbursement of a biosimilar following regulatory approval. The availability of coding and coverage is essential in the US for adoption. CMS, as well as other payers should immediately advance policies that reimburse biosimilars upon FDA approval. This includes the availability of a Q-code as well as pass-through status for biosimilars as soon after regulatory approval as possible.

- **HHS should reconfigure the Medicare Part B Competitive Acquisition Program (CAP)**

  Pfizer supports reviving a voluntary CAP-like model, as we believe the program can be revamped and operated successfully under a simple structure. A carefully constructed version of CAP can help meet the Administration's goal to cut Part B drug spending, and offers an important opportunity to assist in preserving the viability of independent physician practices that play an essential role in the care of Medicare beneficiaries.

  We also believe that a restructured CAP has better prospects of success today than it had in 2006-2008. Changes in how physicians conduct their practices may make the revised CAP more appealing than it was in its first iteration. Physicians are increasingly using specialty pharmacies to deliver drugs for specific patients to their offices for administration. For example, in 2016, 70% of oncology practices used an external specialty pharmacy.[1] Small practices may be drawn to a program like CAP that reduces their inventory costs,[2] which in

[1] A. Fein, The 2017-18 Economic Report on Pharmaceutical Wholesalers and Specialty Distributors, Oct. 2017, at 139 (Wholesalers Report).

[2] Id. at 140 (Practices may "refer patients to specialty pharmacies or utilize an external specialty pharmacy when there would be significant revenue loss for in-practice administration of infusions or injections.").

turn may ameliorate the shift in sites-of-service that is driving up costs for patients and payers.[3] Thus, if implemented with the right incentives and design principles, a simpler restructured CAP may garner broader support than it did during from 2006 to 2008.

To promote the uptake of biosimilars, under the restructured CAP, vendors should be permitted to recommend lower-cost biosimilars to physicians as an alternative to expensive reference biologic products, in accordance with CMS-established guidelines regarding this practice and all applicable laws and regulations. Non-interchangeable biosimilars may not be substituted for a reference biologic product; rather they must be prescribed by a physician. A provision permitting CAP vendors to recommend biosimilars to physicians may help increase prescribing of biosimilars, which could lead to improved uptake of biosimilars and curb increases in prescription drug spending.

We believe that encouraging biosimilar uptake is in the best long-term interest of the Medicare program. We believe that improved biosimilar uptake would result from the pass-through duration extension for biosimilars under the Equitable Adjustment Authority as described above until the sooner of five years after the first pass-through payment or the time at which the average sales price ("ASP") of a particular biosimilar product accumulatively rises faster than inflation.

To help ensure a successful biosimilars marketplace in the US, that will lower healthcare system costs and expand access to patients for these important medicines, it is important that multiple federal and state agencies work individually and collectively to implement policies that will remove barriers to and support the uptake of biosimilars.

2. *FDA uses the Purple Book to provide information about biological products licensed under section 351 of the PHS Act. What additional information or features could be incorporated into the Purple Book to make it more useful to stakeholders, including patients, healthcare providers, pharmacists, and manufacturers?*

Pfizer Comment

Pfizer appreciates FDA's commitment to enhance the Purple Book as outlined in the Biosimilars Action Plan (BAP). Currently, health care professionals (HCPs) have suboptimal awareness of the Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations (the Purple Book). FDA can increase awareness and utility of the Purple Book by taking a number of steps to make the resource more user-friendly for HCPs. Accordingly, Pfizer recommends that FDA take the following actions:

- Merge the two current separate CDER and CBER biologic product lists into one file. The division that licensed the product is not relevant to a HCP; instead, the HCP must be able to find the product that he or she is looking for quickly.

[3] Id. at 132.

- Analogous to the online database that exists for FDA's Orange Book, FDA should consider creating an online database for the Purple Book that is interactive and searchable. As such, we are fully supportive of the development of an enhanced Purple Book as outlined in the BAP. This capability will be valuable to HCPs and other stakeholders as the number of biologic product listings grows. We also recommend that FDA, when constructing such a database, consider the ability and ease of integrating the product information into third-party software.
- Information about biologic products, especially biosimilars, is not optimally integrated into the Purple Book. We recommend that FDA integrate basic biosimilar prescribing and dispensing information directly into the Purple Book or provide a hyperlink to this information. For example, if a user were to click on information in the column "Interchangeable (I)/Biosimilar (B)", the "B" or "I" associated with an individual product listing should provide the definition of what these terms mean, using language similar to what FDA currently provides in its educational material on biosimilars. At a minimum, the information about prescribing and dispensing a biologic product rated "B" or "I" should be referenced in the Purple Book.
- FDA should also consider providing an additional data element for products rated "B", in the form of a notation that indicates whether a single transition from a reference product to a biosimilar had been formally evaluated in the licensure application.
- The Purple Book should clearly note that biosimilars can be prescribed to treatment-experienced patients at the discretion of the HCP given physician-mediated switching is part of usual medical practice and does not require an interchangeability designation. HCPs are not limited to prescribing only biologics designated interchangeable to treatment-experienced patients. Reiterating this messaging in labeling to ensure that HCPs have an accurate understanding of interchangeability would be beneficial.

3. *FDA expects that the number of licensed biosimilar and interchangeable products will continue to increase in the coming years. In many, if not most, cases, FDA anticipates that multiple products will be licensed as biosimilar to, or interchangeable with, a given reference product.*

   What additional steps can FDA take to facilitate the evolution of the biosimilar and interchangeable product marketplace?

   What can FDA do to ensure that confidence in these products among patients, healthcare providers, pharmacists, and other stakeholders will continue to grow?

Pfizer Comment

Combat False and Misleading Marketing Practices

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 mischaracterize important elements of the biosimilar criteria and create doubt and confusion about the safety and efficacy of biosimilars. As noted in the Citizen Petition,[4] Pfizer requests 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. The guidance should also provide examples of communications about biosimilars, including interchangeable biologics, that would not be considered false or misleading.

Increased Education to Address Stakeholder Confusion

Pfizer appreciates FDA's ongoing efforts to develop and release educational materials for health care professionals about biosimilar and interchangeable biological products. The recent series of videos (released May 22, 2018) are informative and may benefit both patients and prescribers. However, we have observed that there continues to be confusion and misinformation on the topics of interchangeability, physician-mediated switching, and pharmacy-level substitution that could hinder confidence in utilization of biosimilars. Thus, we recommend that FDA consider targeting the following topics and concepts in the Agency's educational and awareness initiatives:

- Switching versus Interchangeability. The concept of a single "switch," or transitioning, pertains to a decision made by a treating physician to prescribe a biosimilar (with the patient's knowledge and input) to a patient that had been receiving the reference product. This is distinct from interchangeability, which enables pharmacy level substitution and is supported by data assessing multiple switches. Neither the Biologics Price Competition and Innovation Act (BPCIA), nor any other provision of law suggests or requires that a biosimilar meet the statutory definition of interchangeability as a prerequisite for such a physician-directed treatment decision.

- Interchangeability. It is also essential to avoid inaccurate perceptions of the safety and effectiveness of biological products based on their licensure pathway. A designation of interchangeability should not be communicated as relating to the quality, safety, or effectiveness of the product. It should be clear that a designation of interchangeability in no way suggests that interchangeable products are of a higher quality than biosimilars for the same reference product.

- Totality of Evidence and Extrapolation. Despite ongoing efforts by FDA to educate stakeholders on the basic, overarching concepts related to biosimilarity, many HCPs continue

[4] Citizen Petition from Pfizer Inc. August 22, 2018. FDA-2018-P-3281-0001.

to focus on the clinical data package supporting approval. The expectation for clinical data in multiple, if not all, conditions of use undermines the intention of an abbreviated approval pathway. Continued efforts to educate HCPs and stakeholders on the concepts of "totality of evidence" and "extrapolation" would help build confidence in the biosimilars approval process.

- Patient Education. Although many HCPs are becoming more comfortable with the application and use of biosimilars in clinical practice, some may not be comfortable dialoging with their patients about biosimilars. At the same time, patients want to be involved in their treatment decisions, and educational materials directed towards patients and conversations with their HCPs could be useful. Thus, we recommend that FDA elaborate on its patient-directed materials by developing a brochure describing biosimilars and that includes language regarding initiation with or switching to biosimilars that could be distributed in HCP offices and viewed online by patients.

- Global Regulatory and Patient Experience. HCPs, especially those who are new to working with and prescribing biosimilars, may be more confident with these products if they knew the extent of the experience with biosimilars in Europe. There are 12 years of experience with biosimilars in Europe, spanning over several therapeutic areas, and reflecting no new or unexpected adverse outcomes. A brief mention or review of the real-world experience in Europe with biosimilars in FDA's educational materials could help to facilitate the understanding of how the regulatory requirements to demonstrate biosimilarity leads to the real-world result of no clinically meaningful differences between the reference product and biosimilar.

- Cross-Agency Education Campaign. FDA should work with other governmental agencies, such as CMS and the National Institutes of Health, to create and support a multi-pronged and extensive educational program that can be implemented at the practice and individual patient level by multiple stakeholders (e.g., pharmacists, physicians, nurses, family members, advocacy groups, payers and caregivers). Support should include governmental agencies developing simple educational messages to awarding competitive grants for development of evidence-based best practices for biosimilars education. The government developed educational messages need to be simple and take the approach of "Did you know there is an alternative?" , "Do you know biosimilars are available?", "Biosimilars are as safe and efficacious as their reference products". We recommend that the multi-pronged approach include TV ads and brochures that can be distributed to patients by insurance companies, physicians, and pharmacists.

Naming of Biological Products

Pfizer supports distinguishable nonproprietary naming of biological products in order to facilitate accurate dispensing and effective pharmacovigilance. While FDA has already prospectively implemented the naming convention outlined in the final Guidance for Industry on

Nonproprietary Naming of Biological Products, there has not been progress in retrospective application of the naming convention. Retrospective application of FDA's naming convention to reference products is necessary to help facilitate pharmacovigilance and ensure there are no inaccurate perceptions of the quality, safety, and effectiveness of biosimilars versus their reference products. For example, if a biosimilar product receives a suffix on approval and there has not been retrospective application of a suffix to the reference product the public perception may be that the biosimilar is inferior to the reference product, or perceived as a 'different' therapy. This could hamper the uptake and use of the biosimilar.

4. *Extensive analytical characterization of the proposed biosimilar product and the reference product serves as the foundation for a demonstration of biosimilarity. FDA recognizes that obtaining and testing multiple lots of the reference product adds to the costs of developing a biosimilar product.*

   What can FDA 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?

   FDA is particularly interested in stakeholder comments on

a. *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*

b. *How a 351(k) applicant should account for and evaluate any observed variability in analytical attributes among lots of the reference product or the proposed biosimilar product.*

Pfizer Comment

Reduction in Development Costs Arising from More Focused Use of Analytical Studies and Other Studies on the Reference Product

Pfizer appreciates FDA's efforts towards ensuring efficient global development, and consideration of development cost containment; Pfizer supports continued efforts towards convergence of expectations wherever possible and scientifically appropriate. Presently, FDA requires both comparative analytical data, and a three-arm clinical PK study (U.S.-reference product, non-U.S.-licensed comparator product, proposed biosimilar product) to establish a bridge to the U.S.-licensed reference product, and to allow data derived from studies comparing a proposed biosimilar product with a non-U.S.-licensed comparator to support a demonstration of biosimilarity. FDA should consider, on a case-by-case basis, whether three-arm PK studies are always necessary to establish a bridge to U.S.-licensed reference product. Given that analytical studies allow the direct assessment of quality attributes from licensed products sourced from outside US, this data provides the most sensitive route to demonstrating the direct relevance of

non-U.S.-licensed comparator to the U.S.-licensed reference product. The demonstration of overlapping quality attribute ranges between U.S.-licensed reference product and non-U.S.-licensed comparator provides definitive evidence that the product sources will not impact clinical performance. The expectations of an analytical comparison between licensed product sources should be different from those utilized for a demonstration of biosimilarity: the analytical bridging comparison should focus on the more important, product-specific quality attributes known to impact clinical performance (e.g. high molecular mass species or, when applicable, FcRn binding), utilize only the most robust, sensitive assays and should not automatically include the application of statistical analysis. In contrast, the demonstration of biosimilarity should consider all quality attributes (critical or not), employ multiple orthogonal assessments, and may be complemented with the application of statistical analysis. The segregation of licensed product source assessments, from the biosimilarity assessment, would reduce the unnecessary purchase of multiple licensed product lots just to support orthogonal methods and statistical analysis.

Upon demonstrating that non-U.S.-licensed product is directly relevant to U.S.-licensed reference product, the licensed product data should be pooled to reflect a true representation of the licensed product knowledge in totality. Combined use of U.S.-licensed reference product and non-U.S.-licensed comparator for the development of the quality target product profile of the biosimilar product should be acceptable if bridging has been established; this would further reduce the cost of obtaining reference product for analytical similarity assessments. This approach would also reduce the redundancy of purchasing multiple licensed product lots from multiple countries. FDA could require Sponsors to outline both their testing strategy for licensed products, and the sources they intend to use, in advance, to ensure that the country source and testing plan is appropriate. Refining bridging requirements, and FDA acceptance of non-U.S.-licensed comparator data to support the analytical similarity assessment when bridging has been established, would result in substantial cost savings for biosimilar development programs without compromising FDA's robust scientific standards for licensure.

Assessment of Analytical Similarity

The analytical similarity exercise should start with the definition of the criteria for similarity, and only after this prerequisite can tools such as statistical analysis with some quality attributes, and/or some analytical procedures be considered. Statistical tools provide supportive information in the context of the wider analytical similarity exercise and the statistical analysis results should be combined with other scientific understandings for the final similarity assessment. The principles of ICH Q5E should continue to be applied, namely that predefined criteria should be set to establish similarity, but that any differences that are determined will be assessed for their clinical relevance. If it is possible to demonstrate that differences that defy the predefined criteria are not clinically relevant then similarity may still be established.

Lot and Variability Considerations

The European Medicines Agency has acknowledged "that the manufacturing process of the reference medicinal product evolves through its lifecycle, which may lead to detectable differences in some quality attributes."[5] EMA guidance notes that "the ranges identified before and after the observed shift in quality profile could normally be used to support the biosimilar comparability exercise at the quality level, as either range is representative of the reference medicinal product." FDA is encouraged to consider this approach.

Estimations of the variability of the reference product's quality attributes could be impacted by reference product lot-to-lot variability, or manufacturing changes, over which biosimilar developers have no control. These changes can only be gradually understood via the procurement and testing of multiple lots over an extended period of time that is often well into, or even toward the end of, the biosimilar development program. All reference product lots tested during the development of a biosimilar should be applicable to the analysis of analytical similarity. The reference product variability (especially the variability due to manufacturing changes) should be treated as one of the input factors for similarity acceptance criteria setting.

5. *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. What additional steps can FDA take to facilitate multinational development programs that may include non-U.S.-licensed comparators, to help support development of biosimilar products?*

Pfizer Comment

In addition to comments raised regarding U.S.-licensed reference product under Question 4, FDA is urged to consider the ability to conduct multinational studies, when scientifically justified, to support a demonstration of interchangeability. In the draft guidance for industry, *Considerations in Demonstrating Interchangeability with a Reference Product*, FDA strongly recommends that sponsors use a U.S.-licensed reference product in a switching study (or studies) to support a demonstration of interchangeability. This recommendation may dictate the need to conduct switching studies within the U.S., with consequential impact to feasibility of study conduct. When U.S.-licensed reference product is purchased from wholesalers/agents no supportive documentation is provided as part of the purchase. Supportive documentation includes, for example, Certificates of Analysis, GMP compliance certification, and EU SmPC-like documents that list approved manufacturing sites. Such documentation is essential for the export/import of U.S.-licensed product ex-U.S. in order to support clinical trial applications for

[5] EMA/CHMP/BWP/247713/2012. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues.

the conduct of global clinical studies. In contrast, non-U.S.-licensed product purchased in locations (such as EU) is provided with comprehensive supportive documentation to facilitate the use of the material outside the country of purchase. The recruitment of a switching study solely conducted in the U.S. (where access to biological therapies is greater than in most of the world) is therefore less practical than would be a global program.

The practicality and feasibility of requiring a U.S.-licensed reference product as the comparator in a switching study to support a determination of interchangeability should be carefully considered. We recognize that in the event of actual differences between U.S. and non-U.S. products, this will not be feasible, but in many cases supply chains are global.

6. *FDA expects continued innovation in the biological product marketplace, including innovation during the lifecycle of reference products licensed under section 351(a) of the PHS Act.*

   What can FDA do to ensure that product changes during the lifecycle of reference products (e.g. changes in product presentation) are adequately incentivized without inappropriately deterring competition from biosimilar and interchangeable products, with the overall goal of balancing of innovation and competition?

   Pfizer Comment

   The ability for companies to improve their products is important and in the best interest of public health. Such improvements may relate to, for example, modernization of manufacturing processes, or improvements in device or formulation. However, and as noted in Question 4, the ranges identified before and after an observed shift in quality profile should generally be acceptable to support the analytical biosimilarity exercise, as either range is representative of the reference medicinal product.

   Pfizer notes that to date there is a lack of clarity regarding post-approval manufacturing changes for biosimilars. According to the Biosimilar User Fee Act (BsUFA) II commitment letter the FDA goal to publish draft guidance on Post-Approval Manufacturing Changes for Biosimilar Products is on or before March 31, 2019. Given there are already licensed biosimilars on the market, the FDA is urged to prioritize the release of this draft guidance. Pfizer believes that biosimilar products should have their own life cycle management, and when changes are introduced post-approval a comparability assessment (as described in ICH Q5E) should be performed.

7. *Patents or exclusivity may protect one or more conditions of use (e.g. indications) of the reference product. As a result, 351(k) applicants may seek licensure of the proposed biosimilar product for fewer than all of the conditions of use for which the reference product is licensed. Once a condition of use is no longer protected by patents or exclusivity, FDA anticipates that 351(k) applicants often will seek licensure of their product for this condition of use.*

What challenges do 351(k) applicants face in this context and what should FDA do to achieve the appropriate balance between innovation and competition when one or more conditions of use of the reference product are protected by exclusivity or patents?

Pfizer Comment

Stakeholder Education

FDA should consider providing further educational materials related to biosimilar labeling so that HCPs and other stakeholders may better understand that when an indication is not listed in a biosimilar product's labeling, this can be due to patents or exclusivity blocking approval of that indication, rather than reflecting a scientific judgment by FDA.

Seamless Post-Approval Process to Add Indications

The final guidance for industry, *Labeling for Biosimilar Products* (July 2018) states that a biosimilar product applicant may seek licensure for an additional condition(s) of use of the reference product by submitting a prior approval supplement (PAS) to the 351(k) application that contains the necessary data and information, including draft labeling revised to include the additional condition(s) of use sought. The scenarios FDA provides as examples include situations where the biosimilar product applicant originally obtained licensure for fewer than all of the conditions of use for which the reference product is licensed and situations where the reference product received licensure for a new condition of use for the reference product after the original licensure of the biosimilar product.

A biosimilar product applicant may seek licensure for fewer than all of the conditions of use for which the reference product is licensed due to patents or exclusivity protections, even when extrapolation to the entire range of indications has been scientifically supported. This scenario is acknowledged in the BAP. The BAP notes that "The FDA is developing updated guidance to provide additional clarity to biosimilar applicants who seek approval for fewer than all conditions of use for which the reference product is licensed because, for example, one of the licensed conditions of use of the reference product is protected by a patent." Pfizer urges FDA to consider outlining a process whereby a biosimilar applicant may scientifically justify extrapolation of all conditions of use at the time the 351(k) application is initially reviewed, even if they applicant is not seeking licensure for all conditions of use at that time. This would enable FDA to consider a CBE0 once all protections have expired since the sponsor would have already scientifically justified extrapolation. A PAS should only be required when extrapolation has not yet been scientifically justified. Requiring a PAS in all cases could create unnecessary delays in patient access to biosimilars and hinders the biosimilar sponsor's ability to educate physicians and patients about the additional indication(s) through timely release of promotional materials.

8. *The scope of exclusivity under section 351(k)(7) of the PHS Act may also affect biological product innovation and market entry of biosimilars. Accordingly, FDA seeks comment on the potential application of "umbrella exclusivity" under section 351(k)(7). If umbrella exclusivity were to apply in this context, a biological product that would not be eligible for a new period of exclusivity under section 351(k)(7)(C) would nevertheless be protected for the duration of the exclusivity period for a previously approved reference product. See, for example, 54 FR 28872 at 28897 (July 10, 1989) for an explanation of how umbrella exclusivity functions under the Hatch-Waxman scheme, a related and potentially instructive context. Thus, umbrella exclusivity could help shield certain biological products that would otherwise not be eligible for their own period of exclusivity under section 351(k)(7)(C) from biosimilar competition.*

   What considerations support recognition of umbrella exclusivity under section 351(k)(7), and what considerations disfavor recognizing umbrella exclusivity?

   How would umbrella exclusivity promote biological product innovation, and what effect would it have on market entry of biosimilars?

   What is the relevance and significance, if any, of the patent scheme in considering this issue?

   Pfizer Comment

   In general, FDA should apply umbrella exclusivity in the biologics context in the same manner and to the same extent that FDA applies such exclusivity in the Hatch-Waxman context.

9. *What other challenges have the potential to disrupt the balance between innovation and competition in the biological product marketplace and how can FDA or other stakeholders address these challenges?*

   Pfizer Comment

   Fit for Purpose Clinical Data

   A comparative clinical study is used in a biosimilar application to support a demonstration of biosimilarity (that is, that there are no clinically meaningful differences between a proposed biosimilar product and the reference product). Flexibility in statistical approaches, study endpoints, and overall study design should be considered as a method of speeding up the development process without affecting the ability to detect any clinically meaningful differences that may exist. In addition, different biosimilars to the same reference product should be permitted to individually tailor their data packages and proposed comparative clinical study plans. Where scientifically justified, FDA should be supportive of alternative study designs and statistical approaches.

FDA should also be flexible when considering statistical approaches, study endpoints, and overall study design for interchangeability switching studies. On a case-by-case and individual product basis, and when scientifically justified, FDA should support alternative study designs and statistical approaches that could speed the development process without affecting the ability to ensure that the risk in terms of alternating or switching between use of the interchangeable biologic product and the reference product is not greater than the risk of using the reference product without alternating.

Truthful and Non-Misleading Communications by Biosimilar Product Sponsors

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. It is 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. FDA should clarify in guidance that a biosimilar product sponsor may discuss clinical and other data, notwithstanding whether such data is included in the biosimilar's labeling, with physicians and in promotional materials.

Maximize Review Efficiencies

The FDA Commissioner has been vocal in support of creating a competitive U.S. biosimilar market. However, FDA is struggling with efficient implementation of the biosimilars pathway as evidenced by the small number of recent complete response letters for biosimilar applications for products that already have been given positive opinions by the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP). Efforts to ensure a robust marketplace for biosimilars will not be successful without FDA investment in resources and training, as well as process improvement, to ensure efficient review of 351(k) applications, and improved first-cycle approval rates.

Changes and improvement in the following areas would be helpful in ensuring an efficient review process and increased likelihood of first-cycle approvals:

- **Prioritization of Biosimilars/Appropriate Allocation of FDA Resources.** Biosimilars have an independent user fee structure (the Biosimilar User Fee Amendments of 2017 (BsUFA)) to ensure they are not competing with PDUFA products for Agency resources. BsUFA and PDUFA products are reviewed by the same staff; this is appropriate and allows FDA to leverage the scientific expertise within the Agency to review biosimilar applications. However, FDA must work to

better ensure appropriate allocation of resources, timely implementation of BsUFA II hiring goals, and appropriate training and oversight of new team leaders.

- **Consistency of Standards.** Biosimilar applications should not be held to different data management standards and/or biotherapeutic manufacturing expectations for aspects unrelated to biosimilarity; these requirements should be consistent with those in place for originator (reference) biologic product applications. FDA should consider developing guidance for industry on application requirements relating to manufacturing that provides a detailed outline of expectations applicable to all biotherapeutic applications. This level of transparency in filing expectations would enable more focused discussion with the Agency during formal meetings and provide sponsors with the clarity necessary to ensure applications are complete. It may also reduce the number of complete response letters issued by FDA for biosimilars due to reasons unrelated to similarity.

- **Communication and Transparency.** We recommend that FDA engage in increased communication and transparency during the biosimilar review process to ensure applicants have sufficient time and understanding of issues to address FDA concerns during the review cycle.

We recognize that the goals associated with BsUFA II would directly address many of the areas of improvement identified above, but only if BsUFA II is appropriately implemented. Failure to improve the review process for biosimilars in the near-term will be detrimental to the ultimate success of the biosimilar pathway.

Concluding Remarks

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. 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. Pfizer fully supports the rigorous evaluation standards that FDA applies to all products, including biosimilars so that patients can be assured of the quality, safety and efficacy of these products. As outlined herein, there are opportunities to further optimize the development of biosimilars without compromising scientific standards. Now is the time for a call to action across multiple stakeholders to ensure a successful biosimilars marketplace in the US.

We appreciate the opportunity to present at the September 4th Public Hearing and have appended our presentation to our comment herein. We look forward to future opportunities to provide input as the Agency implements its authority over biosimilars and interchangeable biological products. If you have any questions about these comments please contact Lisa Skeens at (224) 212-4874 or by email at lisa.skeens@pfizer.com .

Sincerely,

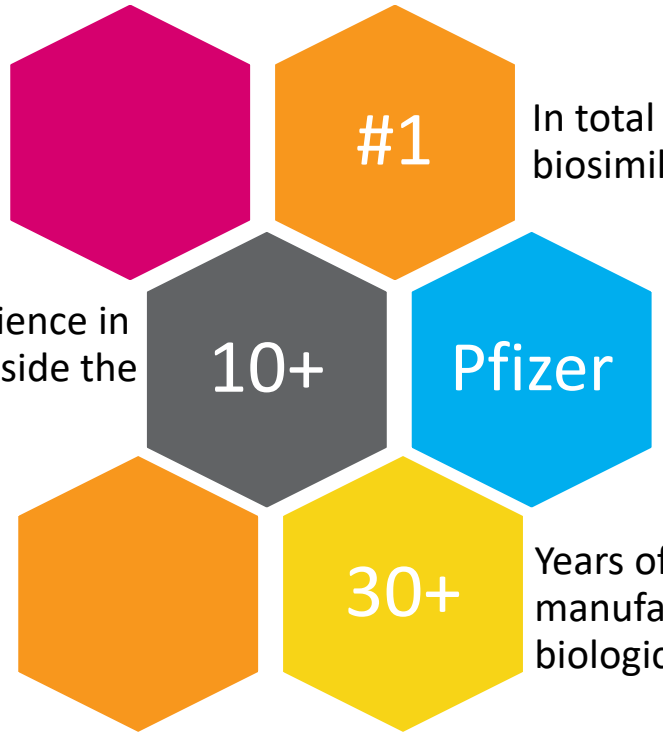
Lisa Skeens, Ph.D.
Vice President, Global Regulatory Affairs

Access to and Acceptability of Biosimilars through Regulatory Reform

September 4, 2018

Pfizer Biosimilars

Pfizer Biosimilars



Our Pipeline [US] As of August 1, 2018

- Licensed

INFLECTRA® (infliximab-dyyb)*	IXIFI® (infliximab-qbtx)	NIVESTYM® (filgrastim-aafi)	RETACRIT® (epoetin alfa-epbx)

- Registration Phase

TRAZIMERA ® (trastuzumab)+

- In Development

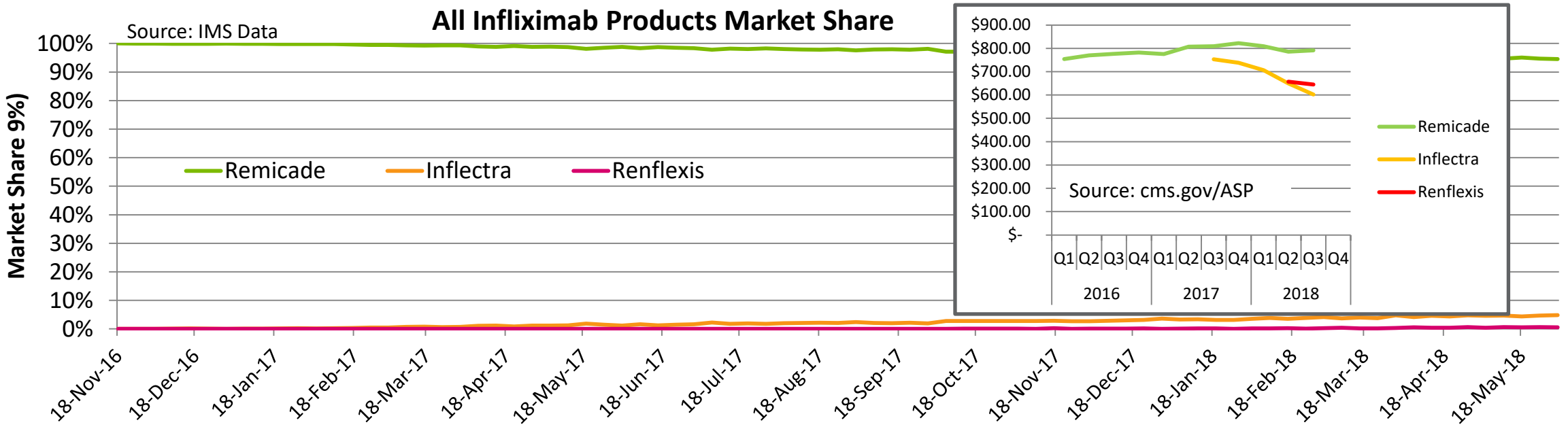
PF-06439535 (bevacizumab)+ PIII	PF-05280586 (rituximab)+ PIII	PF-06410293 (adalimumab)+ PIII
PF-06881894 (pegfilgrastim)+ PI/II		

+5 Assets in pre-clinical development

* Celltrion is license holder; Pfizer is US distributor
\+ Proposed biosimilar to

Pfizer Biosimilars

The Need for Biosimilar Market Access



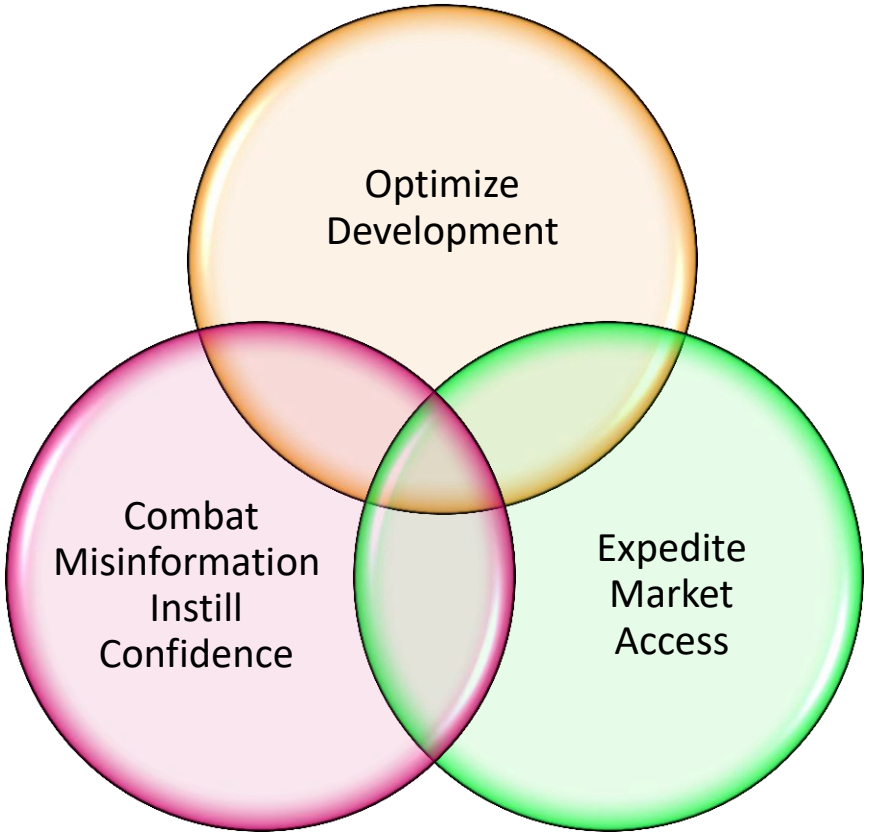
There could be savings of between $523 million and $590 million a year
for commercial payers and Medicare
just by increasing the use of biosimilars for one reference biological product alone [1]

[1] New Study: Patients, Employers and Taxpayers Could Save Significantly if Barriers to Biosimilars Removed. W Winegarden. 2018. Pacific Research Institute. https://www.pacificresearch.org/new-study-patients-employers-and-taxpayers-could-save-significantly-if-barriers-to-biosimilars-removed/

Pfizer Biosimilars

Opportunities to Further Advance Biosimilars

1. Astute Reference Product Bridging
2. Fit for Purpose Clinical Data Package
3. Maximize Review Efficiencies
4. Seamless Post-Approval Process to Add Indications



7. Identify and Eliminate Anti-Competitive Activities

   Implement Policies to Remove Barriers and Advance Uptake

5. Combat Deceptive Marketing Practices

6. Increased Education to Address Stakeholder Confusion

A Successful Biosimilars Marketplace Requires the Support of Multiple Agencies and Stakeholders Working Individually and Collectively

Pfizer Biosimilars

Optimize Development without Compromising Scientific Standards (1)

1. **Astute Reference Product Bridging. Flexibility in bridging expectations and FDA acceptance of non-US-licensed comparator data would enable efficient development and minimize redundant work**
   - On a case-by-case basis, FDA should consider whether three-arm PK studies are necessary to establish a bridge to U.S.-licensed reference product
   - FDA could further consider what degree of analytical bridging is scientifically necessary to establish the relevance of non-U.S.-licensed comparator products to the US market

2. **Fit for Purpose Clinical Data. Flexibility in comparative clinical study (and switching study) statistical approaches, study endpoints, and overall study design should be considered**
   - Different biosimilars to the same reference product should be permitted to individually tailor their data packages and proposed comparative clinical study plans
   - On a case-by-case and individual product basis, and when scientifically justified, FDA should support alternative study designs and statistical approaches that could speed the development process without affecting the ability to detect any clinically meaningful differences (or ensure that there is no greater risk in terms of alternating or switching between products)

Optimize Development without Compromising Scientific Standards (2)

3. Maximize Review Efficiencies. Efforts to ensure a robust marketplace for biosimilars will not be successful without efficient review of 351(k) applications

- FDA must work to better ensure appropriate allocation of resources, timely implementation of BsUFA II hiring goals, and appropriate training and oversight of new team leaders
- FDA should consider developing guidance for industry on application requirements relating to manufacturing that provides a detailed outline of expectations applicable to all biotherapeutic applications
- Timely implementation of The Program under BsUFA II in order to improve communication and transparency during the biosimilar review process is also supported and encouraged

4. Seamless Post-Approval Process. The process to seek licensure for an additional condition(s) of use after product licensure could create unnecessary delays in patient access to biosimilars

- A biosimilar sponsor may seek licensure for fewer than all of the conditions of use for which the reference product is licensed due to patents or exclusivity protections
  - Once all protections have expired FDA should consider a CBE0 appropriate if the sponsor has already scientifically justified extrapolation. A PAS should only be necessary when extrapolation has not yet been scientifically justified

Combating Misinformation & Instilling Confidence

5. **Combat Deceptive Marketing Practices. Deceptive marketing practices create confusion and undermine efforts to enhance stakeholder confidence in biosimilars**
   - HCP and Patient-directed materials and social media disseminated by some reference product sponsors omit or misstate key aspects of the definition of a biosimilar
   - Mischaracterization of the scientific support and appropriateness of physician-mediated switch sow doubt and confusion about prescribing biosimilars to non-treatment naïve patients
   - Mischaracterization of biosimilars without an interchangeable designation as less safe or failing to meet FDA's standard for quality undermines confidence in all biosimilars
   - FDA should take a more active role in preventing originator companies from undermining confidence in biosimilars
   - FDA is urged to issue guidance to help ensure truthful and nonmisleading communications by originator companies about the safety and effectiveness of biosimilars and interchangeable biologics
6. **Increased Education to Address Stakeholder Confusion. Expand Education to provide materials for healthcare providers and pharmacists to have a conversation with their patients**

Pfizer Biosimilars

Expedite Market Access

7. Implement Policies to Remove Barriers and Advance Uptake

- Prohibit the anti-competitive exclusionary contracts and behaviors that create barriers to access for biosimilars
- CMS should publicly track the uptake of biosimilars and cost savings across the Medicare and Medicaid programs
- Medicare & Medicaid plans should support the use of biosimilars
- CMS should expand the 340B pass through for biosimilars both in duration and site of care
- CMS should provide balanced incentives to hospitals and physician practices to use biosimilars
- CMS should proactively educate Medicare and Medicaid beneficiaries on the value of using a lower cost biosimilar to their own pocketbook

Now is the Time for a Call to Action Across Multiple Stakeholders

- **Biosimilars have the potential to save the US healthcare system between $24B and $150B over the next 10yrs** [2]
  - Research shows that if the US increased its use of biosimilar infliximab to cover just 50% of the market, the US would save **over half a billion dollars in one year**[1]……..today, the market share for biosimilar infliximab remains at ~5% almost two years after launch
- **Anti-competitive and deceptive marketing tactics prevent healthcare providers and patients from accessing biosimilars and having confidence in using them**
  - Many patients in the US continue to have limited access to a lower cost biosimilar infliximab through their commercial insurance plan
- **Policies are not in place to drive changes in behavior and uptake of biosimilars**
  - New policies across agencies and stakeholders at the federal, state and private level need to be implemented that will advance the uptake of biosimilars and remove barriers to access

[1] New Study: Patients, Employers and Taxpayers Could Save Significantly if Barriers to Biosimilars Removed. W Winegarden. 2018. Pacific Research Institute. https://www.pacificresearch.org/new-study-patients-employers-and-taxpayers-could-save-significantly-if-barriers-to-biosimilars-removed/

[2] Biosimilar Cost Savings in the United States. AW Mulcahy, JP Hlavka, SR Case. 2017. RAND Corporation. https://www.rand.org/pubs/perspectives/PE264.html

Now is the time for all stakeholders to engage in driving uptake of biosimilars and we thank the FDA for hosting this important public meeting and look forward to continued collaboration in this area

Pfizer Biosimilars