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By Electronic Submission

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Comments on Draft Guidance for Industry Considerations in Demonstrating Interchangeability with a Reference Product [Docket No. FDA–2017–D–0154]

Dear Madam/Sir:

Pfizer Inc (Pfizer) is submitting these comments in response to the Federal Register notice of January 18, 2017 (82 FR 5579-5580) on the Draft Guidance for Industry: *Considerations in Demonstrating Interchangeability with a Reference Product (*"Draft Guidance"*).*

As a manufacturer of both innovator biologic and biosimilar products, Pfizer appreciates the Agency's proactive approach to resolving the many issues and challenges associated with the implementation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). We look forward to future opportunities to provide input as the Agency implements its authority over biosimilars and interchangeable biological products.

Pfizer's comments below include both general comments on interchangeability and the topics raised by FDA in the Federal Register Notice. Pfizer also has specific comments on the Draft Guidance. Beyond the Draft Guidance, Pfizer requests the Agency consider the overall policy landscape for biosimilars as it continues to implement its authorities under the BPCIA and develop and revise guidance. On the one hand, Pfizer appreciates that the Draft Guidance outlines a high bar to meet the additional statutory standard for interchangeability, and yet at the other extreme the agency's draft guidance regarding "Labeling for Biosimilars" seemingly treats biosimilars as generic drugs. Within the biopharmaceutical industry it is understood that these are two very different contexts – guidance relating to product development and how to obtain a regulatory classification is a different matter than labeling where the focus is on appropriate use of a product that has already met the regulatory standard for approval. However, the Agency's approach could appear inconsistent or confusing to or cause misconceptions for the general public. Moreover, these guidance documents could be misconstrued to suggest that biosimilars are either generic drugs (an inappropriate conclusion) or on the other extreme that biosimilars are not appropriate for physician-directed switch without an interchangeability designation (another inappropriate

conclusion). Of course, neither is the case – biosimilars are not generics, and interchangeability is a prerequisite only for substitution at the pharmacy, not for physician-mediated transition. In order to build trust with health care practitioners and patients for successful implementation of the BPCIA and uptake of biosimilars and interchangeable biological products, we request that the Agency consider further educational initiatives. Such initiatives should clarify how FDA's regulatory paradigm, including the various guidance documents, sets appropriate standards to safeguard public health, and define relevant terminology.

I. GENERAL COMMENTS

A. Factors Impacting the Type and Amount of Data and Information Needed to Support a Demonstration of Interchangeability

Section V.A.1. of the Draft Guidance discusses product complexity and the extent of comparative and functional characterization as factors that may influence the data needed to support a demonstration of interchangeability. Pfizer agrees that the product's degree of structural and functional complexity may influence the data and information needed to support a demonstration of interchangeability. However, discussion in the Draft Guidance around extent of comparative and functional characterization may be interpreted to suggest that the highly similar standard is different for interchangeable biological products than it is for biosimilars. To meet the statutory standard to support a demonstration of interchangeability a sponsor must show that the proposed product is biosimilar to the reference product (among other things). The Draft Guidance should be clear that while the extent of analytical similarity will affect overall data requirements in other areas, there is not an additional analytical standard for demonstration of interchangeability.

Analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components are a statutory requirement for demonstration of biosimilarity. Rigorous and comprehensive assessment of comparative structural and functional characterization data, generally including orthogonal methods, are expected to support the demonstration of biosimilarity. Given the already substantial level of analytical data required for demonstration of biosimilarity, it is generally not anticipated that demonstration of interchangeability would require additional analytical studies beyond those supporting biosimilarity.

The term 'fingerprint-like characterization' lacks a clear definition. Pfizer acknowledges the difficulties in defining the term when it is intended to apply broadly to a wide range of biological products. However, the lack of clear definition creates uncertainty for sponsors developing proposed interchangeable biological products and can be manipulated to undermine confidence in biosimilar products. The Draft Guidance states that "a clinically relevant and thus meaningful fingerprint like characterization" may enable a more selective and targeted approach to clinical studies. However, sponsors will be unable to benefit from this in the absence of a clear definition of the term and a timely decision on what this means for their development program relative to the implementation of their clinical program.

Pfizer acknowledges that the Agency may still be developing its thinking on this topic and appreciates that the ambiguity may be intended to ensure that the concept is not restricted and provides sponsors with the opportunity to approach the Agency for consideration of proposals on a case-by-case basis. Pfizer appreciates that the guidance is meant to remain relevant as technology advances and both the Agency and biosimilar developers gain experience in this highly dynamic area of drug development. Nevertheless, if the Agency is unable to provide clarity on the topic of fingerprint-like characterization, the guidance should be revised to acknowledge that this is a forward-thinking concept to be applied based on the critical characteristics of individual products. If the concept of fingerprint-like characterization is to be retained in updated draft or final guidance, then it would be beneficial to provide additional clarity as to how the Agency defines fingerprint-like characterization, how it relates to interchangeability, and how a sponsor may achieve it.

Statements in the Draft Guidance regarding fingerprint-like characterization reducing residual uncertainty may lead to inaccurate perceptions of the quality, safety, and effectiveness of biological products based on their licensure pathway. A designation of interchangeability should not be perceived to relate to the quality, safety, or effectiveness of the product. Rather, this designation denotes that the product has met the statutory standard for substitution without the intervention of the health care provider who prescribed the reference product. If retained in updated or final guidance, it should be clear that the concept of fingerprint-like characterization is intended to be an assessment applied during development in order to inform data expectations. The FDA should ensure guidance does not promote inaccurate perceptions of the quality, safety, and effectiveness of interchangeable products vs biosimilars.

B. Conditions of Use

Pfizer does not interpret, nor do we think that Congress intended, the statutory requirement that sufficient information be provided to show that the biological product can be *expected to produce the same clinical result as the reference product in any given patient* to mean that to secure an interchangeability designation, clinical data in each indication for which the reference product is licensed must be provided. Pfizer thus supports the Agency's approach to having sponsors seeking an interchangeability determination to scientifically justify extrapolation and provide switching data for biological products that are administered more than once to an individual.

However, Pfizer has concerns that the Draft Guidance does not clearly state that a sponsor must provide scientific justification for each condition of use for which the reference product is licensed. Rather, the Draft Guidance states, "The sponsor would need to provide sufficient scientific justification for extrapolating data to support a determination of interchangeability for each condition of use for which the reference product is licensed and for which licensure as an interchangeable product is sought." One could argue that the statutory requirement that the biological product can be expected to produce the same clinical result as the reference product in any given patient has not been met if a biosimilar sponsor were unable

to scientifically support extrapolation of clinical data across each condition of use for which the reference product is licensed.

To address this concern, Pfizer suggests that the Draft Guidance be updated to clarify that a sponsor should provide sufficient data or scientific justification for extrapolating data to support a determination of interchangeability for each condition of use for which the reference product is licensed at the time of the designation request, regardless of whether it seeks licensure as a proposed interchangeable product for fewer than all conditions of use for which the reference product is licensed.

Pfizer believes this would also help mitigate practical implementation concerns should an interchangeable biological product be licensed for fewer than all conditions of use for which the reference product is licensed. Indications are not generally noted on prescriptions, and currently, the Purple Book lists biological products, including any biosimilar and interchangeable biological products, licensed by FDA under the Public Health Service Act but does not delineate indications. Moreover, dispensing often occurs in busy pharmacy settings. In light of these factors, there would be a greater risk of inappropriate substitution if an interchangeable biological product were not demonstrated to be interchangeable for all labeled indications. Nevertheless, we understand there may be situations beyond the proposed interchangeable product sponsor's control that dictate the need to seek licensure for fewer than all reference product conditions of use such as patent- or exclusivity- protected conditions of use. To ensure that even such products can be appropriately substituted without the intervention of the healthcare provider, irrespective of whether the sponsor seeks labeling for all indications for which the reference product is licensed, Pfizer believes that the sponsor should provide sufficient scientific justification to support a determination of interchangeability for each condition of use for which the reference product is licensed.

Proposed Line Edits: [Lines 116-119]
"We ~~note that although a sponsor may seek licensure for a proposed interchangeable product for fewer than all conditions of use for which the reference product is licensed, we~~ **strongly** recommend that a sponsor seek licensure for all of the reference product's licensed conditions of use ~~when possible~~."

Proposed Line Edits: [Lines 525-528]
"The sponsor would need to provide sufficient scientific justification for extrapolating data to support a determination of interchangeability for each condition of use for which the reference product is licensed **at the time of the request for designation regardless of whether licensure for that condition of use** ~~and for which licensure as an interchangeable product~~ is sought."

C. Use of a U.S.-Licensed Reference Product in a Switching Study or Studies

FDA strongly recommends that sponsors use a U.S.-licensed reference product in a switching study (or studies). This recommendation has the potential to create practical challenges with regard to where the study can be conducted. 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/importation of U.S.-licensed product ex-U.S. in order to support clinical trial applications for 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.

Therefore the need for use of U.S.-licensed reference product may dictate the conduct of switch studies within the U.S., with consequential impact to feasibility of study conduct. Given the anticipated size (over 200 subjects), the duration of switching studies, the required stay for intensive pharmacokinetic sampling, and the fact that patients will likely already have access to reference product and biosimilar options on the marketplace, 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 likely impractical. Pfizer urges the Agency to consider the practicality and feasibility of requiring U.S.-licensed reference product as the comparator in a switching study to support a determination of interchangeability. We recognize that in the event of actual differences between the US and non-US products this will not be feasible, but in many cases supply chains are global.

The Draft Guidance suggests that it may be possible for a sponsor to provide scientific justification to support the use of data generated in a switching study using a non-U.S.-licensed comparator to support a demonstration of interchangeability. However, there is not constructive guidance regarding what data and information the scientific justification should include. Pfizer suggests the Draft Guidance be modified to more clearly outline what the Agency's expectations are for scientific justification of use of non-U.S.-licensed comparator.

D. Considerations For Developing Presentations for Proposed Interchangeable Products

Pfizer appreciates the Agency's thoughtful attempt at providing clarity while supporting flexibility regarding interchangeable biological product presentations. The requirements for the Agency's approach to interchangeability support patient safety and the ability of patient/caregiver to readily understand the device they receive via clear labeling, design, and Instructions for Use. Proposed interchangeable product sponsors must demonstrate that the proposed presentation is safe and effective, and that the materials and design are suitable for safe use. This is of particular importance because an interchangeable biological product can be substituted for the reference product without the intervention of the health care provider who prescribed the reference product; therefore, the patient/caregiver must be able to use the interchangeable biological product presentation with minimal acceptable risk of user error that could impact safety or efficacy.

Pfizer has concerns over the proposal for non-inferiority (NI) two-way comparative human factors studies to assess any differences that may not be minor in the design of the

presentation of the proposed interchangeable product. The Draft Guidance states, "A comparative human factors study with an NI design for the purpose of demonstrating interchangeability under section 351(k) of the PHS Act will typically be less complicated than those described in the guidance on NI clinical trials because the endpoints of these NI studies will not be dependent on therapy and the placebo effect will not be a confounding factor." However, behaviors contribute to errors. Moreover, in order to have a subjective and objective assessment of data, potentially large sample sizes will be required to detect differences in the use errors. These studies, as proposed, could be very complicated to implement. Further, percentages of successful use and use error rates are less important than detecting use errors that could result in serious harm, regardless of how infrequently they occur or even if they occur only once in the study. The number of use errors that occur when using a device does not provide evidence, either positive or negative, about the safety or effectiveness of that device unless the causes and potential consequences of those errors are also analyzed.

A risk-based human factors study program can be based on a robust qualitative assessment. This includes identification of critical tasks of use of the proposed interchangeable product, and takes into account design elements that differ from those of the reference product device. Evaluation of use error on critical tasks can be assessed across the relevant user groups: those familiar with the reference product device and those naïve to the product, untrained and trained.

Finally, Pfizer recommends labeling should clearly indicate if the device differs from the reference product device and that Instructions for Use should be carefully read prior to initial use.

E. Physician-Mediated Switching vs. Pharmacy-Level Substitution

The concepts of, and the terminology associated with, physician-mediated switching and pharmacy-level substitution are often confused by stakeholders. The fact that the data required to support a designation of interchangeability is generally referred to as *switch data* or a *switching study* adds to the confusion over these concepts. FDA has not directly addressed the confusion on the topic of physician-mediated switching versus pharmacy level substitution in a manner that would be visible to key stakeholders such as prescribing physicians, payers, and patients.

Interchangeability is a specific statutory designation requiring information showing that the designated product (1) is biosimilar to the reference product ; (2) can also be expected to produce the same clinical result as the reference product in any given patient; and (3) if 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. Interchangeability is defined to mean that the biological product may be substituted for the reference product without the intervention of the prescriber. It is a prerequisite for substitution at the pharmacy level based on a growing body of state laws.

The concept of "switch," or "transition," pertains to a physician's decision regarding which drug to prescribe and is distinct from interchangeability. Neither the 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. Clinical data to support physician-directed decisions to transition a patient from the reference product to the biosimilar are often included as part of the initial 351(k) biological license application for a proposed biosimilar product. The FDA Guidance for Industry*: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* states, "depending on the clinical experience of the reference and proposed products (taking into consideration the conditions of use and patient population), a sponsor may need to evaluate a subset of patients to provide a substantive descriptive assessment of whether a single cross-over from the reference product to the proposed biosimilar would result in a major risk in terms of hypersensitivity, immunogenicity, or other reactions." These data support the clinically relevant scenario where non-treatment naïve patients would transition from the reference product to the biosimilar.

Pfizer urges FDA to directly address confusion related to physician-mediated switching and pharmacy-level substitution in order to ensure appropriate use of terminology such that it is clear that physician –mediated switching is part of usual medical practice and does not require an interchangeability designation. This may best be included in the Draft Guidance Background, General Principles, or Scope sections. As noted earlier, stakeholder education on these concepts will also be essential to the successful and appropriate implementation of the BPCIA.

F. Naming of Interchangeable Biological Products

The Draft Guidance for Industry: *Considerations in Demonstrating Interchangeability with a Reference Product* does not discuss naming of interchangeable biological products. The Guidance for Industry: *Nonproprietary Naming of Biological Products* (2017) describes FDA's current thinking on the naming convention for biological products. Under this naming convention the nonproprietary name for biological products will be a proper name that is a combination of the core name and a distinguishing suffix that is designated by FDA. The final guidance states, "FDA is continuing to consider the appropriate suffix format for interchangeable products."

The Agency notes that distinguishable nonproprietary names will facilitate accurate identification of biological products and pharmacovigilance. It is Pfizer's position that the nonproprietary names of interchangeable biological products should carry a distinguishing suffix in order to support the tracking of product-specific events. A designation of interchangeability, either at initial licensure or subsequently via the filing of a supplement, does not negate the need to clearly identify biological products made by different manufacturers. For example, there could be product quality issues associated with either the reference product or the interchangeable biological product, and different suffixes would

allow these to be handled more appropriately and efficiently. Further, without distinguishable suffixes, post-marketing surveillance data may be less reliable.

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 perceived to relate to the quality, safety, or effectiveness of the product. Rather, this designation is to meet the statutory standard for substitution without the intervention of the health care provider who prescribed the reference product. If FDA were to recommend interchangeable biological products share the same suffix as their reference product then this could lead to inaccurate perceptions of the quality, safety, and effectiveness of interchangeable products vs biosimilars.

For these reasons, it would not be advisable for an interchangeable product to carry the same suffix as designated in the proper name of the reference product. Pfizer urges FDA to seek public comment on naming of interchangeable biological products as they develop their positioning.

G. Labeling of Interchangeable Biological Products

The Draft Guidance does not discuss labeling for interchangeable biological products. Further, specific labeling recommendations for interchangeable biological products are not provided in the draft Guidance for Industry *Labeling for Biosimilar Products* (2015). Pfizer urges FDA to seek public comment on labeling of interchangeable biological products as they develop their positioning.

Pfizer recommends labeling of biosimilar and interchangeable biological products include an "interchangeability statement" that identifies **whether or not** interchangeability has been evaluated and outlines what is meant by interchangeability. It should be clear in labeling that a designation of interchangeability simply denotes that the product has met the statutory standard for substitution without the intervention of the health care provider who prescribed the reference product and does not relate to the quality, safety, or effectiveness of the product. In order to further ensure positioning does not promote inaccurate perceptions of the quality, safety, and effectiveness of interchangeable biological products vs biosimilars FDA should follow the same approach to labeling for interchangeable biological products and biosimilars.

Pfizer believes data generated to support licensure as a biosimilar or interchangeable biological product should be included in product labeling. It is vitally important to build trust with health care practitioners and patients for successful implementation of the BPCIA subsequent use of biosimilars and interchangeable biological products – this is the role of the FDA as well as the manufacturer of specific biosimilar and interchangeable biological products. Inclusion of comparative clinical data (and switching study data were applicable) increases transparency, may advance understanding, and therefore may facilitate safe use of these products. Exclusion of these data could potentially be counter-productive to building trust as trust depends on transparent disclosure of information. Although data may be

accessed in FDA's product reviews on the Drugs@FDA website, it is more appropriately included in the label where information is more readily accessible.

Finally, and where applicable, labeling should clearly indicate that the device may differ than the reference product device and that Instructions for Use should be carefully read prior to initial use.

H. Federal Register Notice Topics for Comment

1. Since the mid-1990s, FDA has approved manufacturing changes for biological products based on data from comparability assessments comparing the pre-change and post-change product using comparative analytical, and, when necessary, animal and/or clinical (e.g., pharmacokinetic, immunogenicity) studies. A demonstration of comparability between pre- and postchange product supports a determination that the safety and efficacy profile remains the same for the product. With respect to interchangeable products, are there considerations in addition to comparability assessments that FDA should consider in regulating postapproval manufacturing changes of interchangeable products? Your comments should include the scientific rationale and justification for your recommendations, as well as recommendations for processes and systems (including key logistics) to implement your recommendations.

Pfizer Comment

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 ICH Q5E[1]) should be performed.

Pfizer recognizes and expects that the standards for post-approval manufacturing changes for interchangeable biological products may be different from those for biosimilars. As Pfizer considered what would be appropriate in regulating post-approval manufacturing changes of interchangeable products we considered what would be in the interest of patient safety, what would be practical to implement, and how to best manage factors beyond the interchangeable product manufacturer's control (ie reference product sponsor manufacturing decisions). The

[1] Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process. Adopted by CPMP, December 2004, CPMP/ICH/5721/03.

ability for companies, including interchangeable biological product manufacturers, 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.

Pfizer recommends FDA consider the following when regulating post-approval manufacturing changes of interchangeable products:

- Mandatory use of comparability protocols – implementing any (non-minor) CMC post-approval change of an interchangeable biological product should require the submission of a comparability protocol containing a prospective outline of
    - The planned change(s)
    - A risk assessment of the proposed change(s) – impact to product quality and potential clinical impact
    - The analytical procedures to assess analytical pre- and post-change comparability of quality attributes
    - The acceptance criteria against which comparability will be confirmed – acceptance criteria should be based on the product profile that was included in the license application for the proposed interchangeable product

Pfizer considers the advantages of this approach are as follows:

- It utilizes established regulatory framework, avoiding the requirement to generate new or unique approaches to the lifecycle management of interchangeable biological products
- Retains the philosophy and approach established in ICH Q5E, whilst ensuring prospective FDA review of all proposed changes for interchangeable biological products
- Any deviation from the agreed comparability plan, or failure to meet approved acceptance criteria, would require FDA assessment, and in keeping with philosophy established in ICH Q5E could require additional studies
- Ensures FDA oversight of all non-minor post-approval changes to interchangeable biological products, proactively ensuring the comparability plan is appropriately comprehensive (which may include analytical comparability, or may in some cases extend to PK comparability and enhanced pharmacovigilance (PV) assessment)
- Allows the interchangeable biological product and its reference product to maintain separate life cycle management without impacting patient safety (continued comparison to the reference product in real time is not required)

2. As explained in the guidance ''Considerations in Demonstrating Interchangeability with a Reference Product,'' FDA expects that sponsors seeking an interchangeability determination will submit data and information to support a showing that the proposed interchangeable product can be expected to produce the same clinical result as the reference product in all of the reference product's licensed conditions of use. How, if at all, should the Agency consider conditions of use that are licensed for the reference product after an interchangeable product has been licensed? Your comments should include the scientific rationale and justification for your recommendations, as well as recommendations for processes and systems (including key logistics) to implement your recommendations.

Pfizer Comment

One can imagine there will be many scenarios in which the reference product is licensed for a new condition of use after a request for a designation as interchangeable has been submitted. Pfizer suggests that the Agency consider each situation on a case-by-case basis in direct communication with the interchangeable product sponsor. Generally, and within a reasonable period of time, an interchangeable product sponsor should be required to make a regulatory submission to provide sufficient data or scientific justification for extrapolating data to support a determination of interchangeability for any condition of use that is licensed for the reference product after the request for an interchangeability designation has been submitted. The scientific justification for extrapolation should address factors outlined in the Draft Guidance (Lines 519-558).

SPECIFIC COMMENTS

Line No.	Comment and Rationale	Proposed change (if applicable)
General Comment	The Draft Guidance only considers the statutory framework which contemplates that the interchangeable biological product may be substituted *for the reference product* without the intervention of the health care provider. The FDA does not directly address the relevant scenario where multiple interchangeable biological products may be on the marketplace. The Draft Guidance also does not explicitly state that non-interchangeable biosimilars should not be substituted without the intervention of the prescriber. It is understood that state laws will govern the substitution of medicines. However, FDA recommendations could help inform state law implementation.	The Agency has stated on the Purple Book website that "FDA expects that a biosimilar product will be specifically prescribed by the healthcare provider and cannot be substituted for a reference product at the pharmacy level." Pfizer recommends that this statement be included in the Draft Guidance Background, General Principles, or Scope sections in order to aid in appropriate implementation of biosimilar and interchangeable biological product designations.
General Comment	The concepts of and terminology associated with physician-mediated switching and pharmacy-level substitution are often confused by stakeholders and not addressed in guidance. See Section I. General Comments D. Physician-Mediated Switching vs. Pharmacy-Level Substitution	Pfizer urges FDA to directly address this confusion in order to ensure appropriate use of terminology, and appropriate application of biosimilar and interchangeable biological product designations. This may best be included in the Draft Guidance Background, General Principles, or Scope sections. Stakeholder education on these concepts will also be essential to the successful and appropriate implementation of the BPCIA.
General Comment	Suffix format for interchangeable products remains unclear. It would not be advisable for an interchangeable product to carry the same suffix as designated in the proper name of the reference product. See Section I. General Comments E. Naming…	FDA should provide guidance on the suffix format for interchangeable biological products.

Line No.	Comment and Rationale	Proposed change (if applicable)
General Comment	Specific labeling recommendations for interchangeable biological products are not provided in any guidance to date. Pfizer recommends labeling for biosimilars and interchangeable biological products should include an "interchangeability statement" that identifies **whether or not** interchangeability has been evaluated and outlines what is meant by interchangeability. See Section I. General Comments F. Labeling…	FDA should provide guidance on labeling for interchangeable biological products.
116-119	The Draft Guidance states a sponsor may seek licensure for a proposed interchangeable product for fewer than all conditions of use for which the reference product is licensed. See Section I. General Comments B. Conditions of Use	~~*We note that although a sponsor may seek licensure*~~ *For a proposed interchangeable product* ~~*for fewer than all conditions of use for which the reference product is licensed, w*~~***e strongly*** *recommend that a sponsor seek licensure for all of the reference product's licensed conditions of use* ~~*when possible*~~*.*

Line No.	Comment and Rationale	Proposed change (if applicable)
General Comment 186-227 246-258	• The Draft Guidance should be clear that there is not an additional analytical standard for demonstration of interchangeability. • The term fingerprint-like similarity lacks a clear definition. • Statements in the Draft Guidance regarding fingerprint-like characterization reducing residual uncertainty may lead to inaccurate perceptions of the quality, safety, and effectiveness of biological products based on their licensure pathway. See Section I. General Comments A. Factors Impacting the Type and Amount of Data…	• If the concept of fingerprint-like characterization is to be retained in updated draft or final guidance, then it would be beneficial to provide additional clarity as to how the Agency defines fingerprint-like characterization, how it relates to interchangeability, and how a sponsor may achieve it. • The FDA should ensure the Draft Guidance does not inadvertently create inaccurate perceptions of the quality, safety, and effectiveness of interchangeable products vs biosimilars.
288-302	This section of the document is titled to discuss postmarketing *data that may impact* the need for additional data while the suggestion of an additional study would be clinical *data needed to support* demonstration of interchangeability. Section header should be updated to reflect the content of the section.	Suggest changing header from *Biosimilar Product Postmarketing Data That May Impact the Data Needed to Support a Demonstration of Interchangeability* to *The Role of Biosimilar Product Postmarketing Data* so it is more clear what this section relates to
291-294 [254-255]	The Draft Guidance states: "Further, there may be situations where a postmarketing study, in addition to postmarketing surveillance data, from the licensed biosimilar product may be needed to address residual uncertainty regarding a demonstration of interchangeability." It is at a sponsor's discretion whether or not to seek an interchangeability designation. The term postmarketing study could be confused to mean a postmarketing requirement or commitment. It seems the Agency is suggesting that under certain circumstances additional clinical data beyond postmarketing surveillance data and switching study data may be required.	Lines 291-294 *Further, there may be situations where* ***clinical study safety data*** ~~*a postmarketing study*~~*, in addition to postmarketing surveillance data, from the licensed biosimilar product may be needed to address residual uncertainty regarding a demonstration of interchangeability.* Accordingly, Lines 254- 255 should be modified as follows: *Here, postmarketing data for the product as a licensed biosimilar, in addition to an appropriately designed switching study,* ***and other clinical*** *or other data-sources such as pragmatic study data or real world evidence* ***if necessary*** *(see section VI.A)….*

Line No.	Comment and Rationale	Proposed change (if applicable)
General Comment Switching Study	The FDA draft "Guidance for Industry on Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations" recommends (2014, lines 947-948): "….that the assayed drug content of the test product batch not differ from the reference product by more than +/- 5 percent." Pfizer suggests adding a similar statement to this Draft Guidance to allow for greater control over impact of lot variability on PK.	
325-327 416-481	The Draft Guidance states: "A switching study or studies should evaluate changes in treatment that result in two or more alternating exposures (switch intervals) to the proposed interchangeable product and to the reference product." "The switching arm is expected to incorporate at least two separate exposure periods to each of the two products (i.e., at least three switches with each switch crossing over to the alternate product)." The use of the terms of "*at least"* and "*two or more,"* implies that there could be scenarios where additional switches could be required. However, it is unclear what considerations determine the number of exposure periods.	Please clarify what considerations determine the number of exposure periods. A graphic depicting study schema would also be helpful.
447-470	The Draft Guidance should be organized to ensure that it is clear which aspects of dedicated switching study designs also apply to integrated study designs. For example, it is presumed that lines 390-445 under Section VI.A.2.a. Dedicated Switching Study Design are (and should be) applicable to Section VI.A.2.b. Integrated Study Design. However, as currently organized this is not entirely clear and only the powering of an integrated study is explicitly discussed.	Section VI.A.2 should be reorganized to highlight the two switching study design options, then clearly outline the information in lines 390-445 as applicable to all switching studies regardless of whether they are dedicated or integrated.

Line No.	Comment and Rationale	Proposed change (if applicable)
525-528	If a biosimilar sponsor were unable to scientifically support extrapolation of clinical data across each condition of use, one could argue that the statutory requirement that the biological product "*can be expected to produce the same clinical result as the reference product in any given patient"* has not been met and therefore such a product would not be eligible for an interchangeability designation. The Draft Guidance should be updated to clarify that the statutory requirement mandates that a sponsor seeking an interchangeability designation provide sufficient scientific justification for extrapolating data to support a determination of interchangeability for each condition of use for which the reference product is licensed, regardless of whether it seeks licensure as a proposed interchangeable product for fewer than all conditions of use for which the reference product is licensed.	"The sponsor would need to provide sufficient scientific justification for extrapolating data to support a determination of interchangeability for each condition of use for which the reference product is licensed **at the time of the request for designation regardless of whether licensure for that condition of use** ~~and for which licensure as an interchangeable product~~ is sought."
561-612	The Draft Guidance suggests that it may be possible for a sponsor to provide scientific justification to support the use of data generated in a switching study using a non-U.S.-licensed comparator to support a demonstration of interchangeability. However, there is not constructive guidance regarding what data and information the scientific justification should include. See Section I. General Comments C. Use of a U.S.-Licensed Reference Product…	Pfizer suggest the Draft Guidance be modified to more clearly outline what the Agency's expectations are for scientific justification of use of non-U.S.-licensed comparator.
707-709	The sentence below is repetitive with Lines 702-704 "The external critical design attributes of the product would be those features that end users rely on to perform the tasks identified as critical to the appropriate use of the product."	Suggest revising paragraph to eliminate redundancies.

Line No.	Comment and Rationale	Proposed change (if applicable)
786-802	The Draft Guidance states: "*FDA views a design difference in product presentation as minor if the differences in the user interface of the proposed interchangeable product, in comparison to the user interface of the reference product, do not affect an external critical design attribute.*" This section goes on to note that minor differences are likely to be viewed as acceptable if the sponsor can submit information, for example from threshold analyses, to demonstrate that the differences in design do not impact appropriate use.	"*FDA views a design difference in product presentation as minor if the differences in the user interface of the proposed interchangeable product, in comparison to the user interface of the reference product, do not affect an external critical design attribute* ***that could negatively impact appropriate use***."
793-794	"*...differences in design do not involve an external critical design attribute that could negatively impact appropriate use.*" These two statements are somewhat contradictory.	

We appreciate the opportunity to comment on this draft guidance. If you have any questions about these comments, please contact Laura McKinley at 212-733-8861 or by email at laura.m.mckinley@pfizer.com.

Sincerely,

Laura McKinley

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