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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Subject: FDA-2017-D-0154: Considerations in Demonstrating Interchangeability With a Reference Product

Dear Sir/Madam:

As a developer and manufacturer of both innovative and biosimilar medicines with more than 35 years of experience in the biotechnology industry, Amgen applauds FDA's leadership in progressing a science-based pathway for designating biosimilars as interchangeable. We believe the success of the nascent US biosimilar market hinges upon the confidence in and use of these medicines, which will be supported by scientifically sound principles for approval, accurate prescribing and dispensing, and appropriate use of these products.

We are pleased to have the opportunity to offer comments on the Draft Guidance for Industry on Considerations in Demonstrating Interchangeability with a Reference Product. We have included our comments on relevant sections in an effort to support the FDA in this endeavor.

Sincerely,



Steven K. Galson, M.D., M.P.H.
Senior Vice President, Global Regulatory Affairs and Safety
Amgen, Inc

ENCLOSURE: Amgen Comments on: FDA Draft Guidance for Industry on Considerations in Demonstrating Interchangeability with a Reference Product

AMGEN COMMENTS to FDA docket on draft guidance on demonstrating interchangeability

Amgen is a global biotechnology and pharmaceuticals company based in Thousand Oaks, CA. We appreciate FDA's development and implementation of important policies for biosimilars and welcome the opportunity to offer comments on the recently issued draft guidance on *Considerations in Demonstrating Interchangeability with a Reference Product*.¹

In the following comments, we address specific sections of the draft guidance, followed by some additional issues for consideration with regard to interchangeability. Lastly, we address the two questions posed by FDA in the Federal Register.¹ We respectfully request that FDA address the considerations outlined herein prior to issuing final guidance. In particular, we ask that FDA:

1. Make clear that interchangeable designations apply only to the relationship between an interchangeable product and its reference product;
2. Ensure clear labeling with respect to the designation of interchangeability (both product and presentation specific) and inclusion of clinical information supporting the interchangeability designation;
3. Make the recent nonproprietary naming framework outlined in recent guidance applicable to interchangeable products; and
4. Establish an appropriate mechanism to reclassify an interchangeable to a biosimilar, should the need arise.

I. SECTION-BY-SECTION COMMENTS ON THE DRAFT GUIDANCE

A. "GENERAL PRINCIPLES"- (Section III of the Draft Guidance, pages 2-4)

FDA's proposed framework for designating a biosimilar product as interchangeable with its reference product as articulated in the draft guidance is appropriately robust and science-based.¹ A central doctrine in healthcare, which underpins the approach taken when treating patients, is that evidence should precede practice. FDA has upheld this principle by recommending the generation of data to support appropriately rigorous and scientifically grounded evidence as the basis for a demonstration of interchangeability.

FDA has proposed that data necessary to support an interchangeability designation may depend on the nature of the product and should be evaluated on a case-by-case basis. Biosimilars shown to exhibit a very high degree of analytical similarity to their reference product, with very little or no residual uncertainty, and that exhibit a historically low risk of immunogenicity, *may* be adequately shown to be interchangeable by a single, well-designed, clinical switching trial; whereas molecules that are inherently more difficult to characterize and that retain greater residual uncertainty as to analytical similarity could require additional evidence to support a demonstration of interchangeability. While analytical techniques have advanced significantly, they cannot characterize all relevant structural and functional differences between two biological products,² and they do not serve as reliable surrogates for predicting patient response and/or immunogenicity. Thus, in order to fully address interchangeability in a scientifically appropriate manner, some degree of clinical testing should always be conducted to provide a robust assessment of immunogenicity and direct information about patient safety.

¹ FDA Draft Guidance for Industry, Considerations in Determining Interchangeability with a Reference Product, 82 Fed. Reg. 5579 (Jan. 18, 2017).

² See FDA, Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015), at p. 5.

The draft guidance states that “we recommend that a sponsor seek licensure for all of the reference product’s licensed indications of use, when possible.”³ With the exception of indications protected by exclusivity or patent, Amgen believes biosimilar applicants should be *required* to seek licensure for all of the reference product’s licensed indications in order to obtain an interchangeability designation. Prescribers and pharmacists have as their dominant point of reference the generic drug paradigm under which drugs are rated as therapeutically equivalent across all indications. This rating is perceived as reflecting FDA’s scientific judgment, even though the labeled indications of the generic product and reference product may differ for legal reasons.⁴

A similar assumption of interchangeability across indications is not appropriate for a biosimilar absent adequate scientific justification to support interchangeability for each indication. For the safety of patients and to avoid inappropriate substitution, FDA should anticipate that prescribers and pharmacists may apply their experience with generics to biologics, and therefore assume an interchangeability designation generally applies for all uses of the product. Further, under the laws of states that have enacted legislation addressing biosimilar substitution, a patient may receive an interchangeable product through substitution, regardless of the specific indication for which the healthcare provider prescribed the reference product. Therefore, we request that FDA *require* a sponsor seeking an interchangeable designation to seek licensure in all *legally available* indications, and to provide scientific evidence that the interchangeable designation is applicable to *all* indications, including those for which the biosimilar may not be licensed for reasons of exclusivity or intellectual property protection.

The guidance also states that the “main purpose of a switching study is to demonstrate that the risk in terms of safety or diminished efficacy of alternating or switching between use of the proposed interchangeable and the reference product is not greater than the risk of using the reference product without such alternation or switch.”⁵ Therefore, clinical switching studies with the goal of demonstrating interchangeability should be designed and powered to detect subtle changes in patient response. Clinical studies that utilize pharmacokinetic (PK) and pharmacodynamic (PD) parameters, as well as sensitive measures of immunogenicity, should be an integral part of a program aimed at demonstrating interchangeability.⁶ For a product already licensed as a biosimilar, switching data derived from real-world evidence may serve as supportive information when assessing a potential designation as an interchangeable product, but such data alone would not be scientifically adequate to support an evaluation of switching between a reference product and a proposed interchangeable product. As real world data are observational in nature, it would not bring the necessary rigor and cannot replace a well designed clinical study.^{7,8}

B. “FACTORS IMPACTING THE TYPE AND AMOUNT OF DATA AND INFORMATION NEEDED TO SUPPORT AN INTERCHANGEABILITY DETERMINATION” - (Section V of the Draft Guidance, beginning at page 5)

1. Product Complexity and the Extent of Comparative and Functional Characterization

On the topic of *Product Complexity and the Extent of Comparative and Functional Characterization*,⁹ FDA’s recommendation of a step-wise approach to address residual uncertainty in assessing interchangeable products is scientifically sound and robust. However, the impact of molecular complexity on immunogenicity should not be overgeneralized. There are many factors beyond molecular complexity

³ FDA, Draft Guidance for Industry: Considerations in Determining Interchangeability with a Reference Product (Jan. 2017), at p. 4.

⁴ 21 U.S.C. § 355(j)(2)(A)(viii).

⁵ FDA, Draft Guidance for Industry: Considerations in Determining Interchangeability with a Reference Product (Jan. 2017), at p. 9.

⁶ FDA, Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Apr. 2015), at p 15.

⁷ FDA, Draft Guidance for Industry: Use of Real-World Evidence to Support Regulatory Decision Making for Medical Devices (Sept. 2016), at p. 8.

⁸ Sherman RE, et al. Real-World Evidence – What it is and What it Can Tell Us. *N Engl J Med*, 2016; 375:2293-2297.

⁹ FDA, Draft Guidance for Industry: Considerations in Determining Interchangeability with a Reference Product (Jan. 2017), at p. 5.

of the product that can affect immunogenicity.¹⁰ These factors may be product related, process related, or patient related,¹¹⁻¹⁷ and all should be considered when evaluating risk to patients.

In the context of comparative analytical characterization, the draft guidance refers to “fingerprint-like characterization” and “fingerprint-like analytical similarity.”¹⁸ FDA has used the term “fingerprint-like similarity” in other guidance documents as well,^{19,20} but there is not yet a real-world example of a biosimilar that has been shown to exhibit “fingerprint-like similarity”. FDA’s clinical pharmacology guidance describes fingerprint-like similarity as the “results of integrated, multi-parameter approaches that are extremely sensitive in identifying analytical differences.”²⁰ Amgen requests that FDA further clarify the definition of, and the criteria necessary for a biosimilar to obtain, a fingerprint-like similarity classification. Furthermore, additional clarity is requested regarding phrases such as “a very high level of confidence” and “integrated, multi-parameter approaches”²¹; an example of such approaches would be very useful to sponsors.

2. Product-Specific Immunogenicity Risk

On the topic of *Product-Specific Immunogenicity Risk*,²² we note that current analytical methods, though extremely sensitive, are not capable of relating physico-chemical properties of a therapeutic protein to a clinical response. They are also incapable of predicting the effect of product-related factors on immunogenicity. Therefore, the results of comparative analytical similarity studies alone should not serve as a surrogate for sensitive measures of immunogenicity in patients. In particular, Amgen requests that FDA more clearly describe its position on the potential differences in approaching the assessment of immunogenicity. For example, less complex molecules, with a well-defined mechanism of action and low risk of adverse events, may indeed pose a lower risk to patients in a clinical setting where switching between a reference product and an interchangeable product are practiced. However, due to the variable causality of immunogenicity,¹¹⁻¹⁷ this risk, at a minimum and irrespective of molecular complexity, should be fully confirmed in a clinical switching trial using appropriate PK endpoints with sensitive measures of immunogenicity that quantify its impact on efficacy. In addition, the potential for immunogenicity increases with the duration of therapy,²³ depending on the product. Therefore, FDA should consider the duration of treatment when assessing the necessary information required to address product-specific immunogenicity risk.

¹⁰ Bandyopadhyay A., Complexities of Protein Therapeutics and Immunogenicity. *J Bioana Biomed*, 2015; 7:3:70-74.

¹¹ Test ST et al. Increased immunogenicity and induction of class switching by conjugation of complement C3d to pneumococcal serotype 14 capsular polysaccharide infect. *Immunol*, 2001; 69: 3031- 3040.

¹² Schellekens H. Immunologic mechanisms of EPO-associated pure red cell aplasia. *Best Pract Res Clin Haematol*, 2005; 18: 473-480.

¹³ Hay M, et al. Bio/Biomed tracker clinical trial success rates study, BIO CEO & Investor Conference, BIO February 15th, 2011.

¹⁴ Chirino AJ et al. Minimizing the immunogenicity of protein therapeutics. *Drug Discov Today*, 2004; 9: 82-90.

¹⁵ De Groot AS and Martin W. Reducing risk, improving outcomes: bioengineering less immunogenic protein therapeutics. *Clin Immunol*, 2009; 131: 189- 201.

¹⁶ Moore WV and Leppert P. Role of aggregated human growth hormone (hGH) in development of antibodies to hGH. *J Clin Endocrinol Metab*, 1980; 51: 691-697.

¹⁷ Braun A, et al. Protein aggregates seem to play a key role among the parameters influencing the antigenicity of interferon alpha (IFN-alpha) in normal and transgenic mice. *Pharm Res*, 1997; 14: 1472-1478.

¹⁸ FDA, Draft Guidance for Industry: Considerations in Determining Interchangeability with a Reference Product (Jan. 2017), at p. 6.

¹⁹ FDA, Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product, Guidance for Industry (April 2015), at p. 8.

²⁰ FDA, Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (Dec. 2016), at p. 6.

²¹ FDA, Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (Dec. 2016), at p.6.

²² FDA, Draft Guidance for Industry: Considerations in Determining Interchangeability with a Reference Product (Jan. 2017), at p. 7.

²³ Kuriakose A, et al. Review Article: Immunogenicity of Biotherapeutics: Causes and Association with Posttranslational Modifications. *J Immun Res*, 2016.

C. “DATA AND INFORMATION NEEDED TO SUPPORT A DEMONSTRATION OF INTERCHANGEABILITY” - (Section VI of the Draft Guidance, beginning at page 9) *Considerations for the Design and Analysis of a Switching Study or Studies Needed to Support a Demonstration of Interchangeability (Section VI.A of the Draft Guidance)*

1. “Study Endpoints” (beginning at page 10)

The clinical switching study design should account for how the proposed interchangeable product will be used in clinical practice, including dosing frequency, sensitivity of the patient population, time between alternations, washout periods, etc., and is appropriately addressed in the draft guidance. Clarification is requested, however, for the following statement: “[f]or biological products that are not intended to be administered to an individual more than once, FDA expects that switching studies would generally not be needed.”²⁴ For scientific reasons, “not intended to be administered to an individual more than once” should be clarified to mean that no more than a single administration of a product would be expected over the entire course of treatment. In the context of multiple treatment cycles, the possibility of latent immunogenicity exists, and thus consideration of this protocol as a “single administration” would not be appropriate.

2. General Comments on Clinical Trial Design (beginning at page 10)

The scientific considerations described in this section with respect to the design of a multi-switch study, the study analysis, and the proposed integrated study design are appropriate, and the recommendation by FDA to use *adequately sensitive patients* in the study design is scientifically sound and clinically relevant. Additionally, we agree that the conditions of use to be studied should support extrapolation to other conditions of use as demonstrated to be appropriate, and the route of administration (ROA) chosen for clinical studies should represent the most appropriate ROA in order to anticipate clinical implications related to immune response. This is typically subcutaneous administration in that the skin and the mucosa may carry the greatest potential for an immunological response.²⁵ At the Agency’s discretion, and based on the historical immune response associated with the reference product, it may be necessary for multiple ROAs to be addressed in the clinical trial program for products seeking an interchangeable designation.

3. “Extrapolation of Data” - (Section VI.B of the Draft Guidance, beginning at page 14)

The draft guidance states that “The sponsor would need to provide sufficient scientific justification for extrapolating data to support a determination for interchangeability for each condition of use for which the reference product is licensed and for which licensure as an interchangeable is sought.”²⁶ We point out that while sponsors may not seek licensure for all indications of the reference product (either by choice or as a result of intellectual property protections for certain indications), in the case of interchangeability, it would be appropriate for FDA to require sponsors to adequately demonstrate that the product can be used in *any and all* conditions of use for which the reference product is licensed, *including protected indications*. Although licensure for a particular indication may not be permitted at the time the product is first designated as an interchangeable product, it is reasonable to expect that physicians will assume products designated as such are interchangeable for all indications. Additionally, exclusivities expire, and it would be expected that data submitted to support an interchangeable designation would be used as scientific justification for extrapolation to the newly available indications. The criteria laid out under this section of the draft guidance provides a strong scientific foundation for sponsors to appropriately demonstrate such scientific justification.

²⁴ FDA, Draft Guidance for Industry: Considerations in Determining Interchangeability with a Reference Product (Jan. 2017), at p. 9.

²⁵ Chirino AJ et al. Minimizing the immunogenicity of protein therapeutics. *Drug Discov Today*, 2004; 9: 82-90.

²⁶ FDA, Draft Guidance for Industry: Considerations in Determining Interchangeability with a Reference Product, (Jan.2017), at p. 14.

D. “USE OF A U.S.-LICENSED REFERENCE PRODUCT IN A SWITCHING STUDY OR STUDIES” - (Section VII of the Draft Guidance, beginning at page 15)

The use of the U.S.-licensed reference product when conducting clinical switching studies between the proposed interchangeable product and reference product is appropriate given the purpose of the studies. While all approved biosimilars are deemed to be safe and effective, they may not have been evaluated for purposes of risk presented from multiple switches. Since the difference between two products is a factor that may trigger an immune response, testing with the actual product used in clinical practice in the U.S. will be fundamental to answering the question of the risks associated with switching between the two products.

E. “CONSIDERATIONS FOR DEVELOPING PRESENTATIONS FOR PROPOSED INTERCHANGEABLE PRODUCTS” - (Section VIII of Draft Guidance, beginning at page 16)

1. *General Considerations – (Section VIII.A of the Draft Guidance, beginning at page 17).*

FDA indicates in the draft guidance that sponsors seeking an interchangeability designation may elect to pursue licensure of only a subset of presentations licensed by the reference product. This may be appropriate given that it is likely a biosimilar will lag behind the reference product in the development and approval of new presentations. However, while a sponsor seeking an interchangeable designation may not be *required* to pursue licensure of all the presentations licensed by the reference product, the sponsor should be required to obtain an interchangeable designation for *all* presentations that will be marketed. Allowing a product to exist in the marketplace as both an interchangeable and a biosimilar may cause confusion among providers and dispensers, a risk that can likely be mitigated by ensuring that all presentations marketed by the interchangeable sponsor are deemed interchangeable with the reference product.

We strongly urge FDA to ensure that the designation of interchangeability for every product be specific to which reference product presentation(s) are served by the biosimilar. This will facilitate prescriber use and proper pharmacy dispensing of interchangeable products. Easy access to this information will be important; the biosimilar label and the “Purple Book” should include information on available presentation(s) and interchangeability status. This is in line with pharmacists’ regular use of FDA’s “Orange Book” to assess therapeutic equivalence ratings for generics. In order to minimize the risk for medication and/or administration errors, the available presentations and the fact that they are all deemed interchangeable with the corresponding reference product presentations should be clearly noted in the “Purple Book.”

In addition, we ask that FDA provide guidance on the expectations for a proposed interchangeable product sponsor when there is a change in the reference product presentation (e.g. design changes, software user interface updates, etc.) that corresponds to a presentation in which the interchangeable product is marketed. Amgen believes that, in such a case, to ensure patient safety and to maintain the designation of a biosimilar as an interchangeable product, the interchangeable product sponsor should, at a minimum and within a reasonable amount of time, conduct a new threshold analysis and submit that analysis to FDA for review to determine if additional human factors evaluation is warranted.

2. *Analysis of Proposed Presentations of Proposed Interchangeable Products - (Section VIII.B of the Draft Guidance, beginning at page 18).*

Amgen supports comprehensive and robust human factors requirements to ensure that the proposed interchangeable product presentations are interchangeable with the reference product presentations. These requirements should be in addition to the current expectations for receiving a biosimilar designation (i.e. human factors validation studies to demonstrate safety and effectiveness for the

intended users, uses, and use environments),²⁷ as there may be additional use risks specific to interchangeable use that are not associated with a biosimilar.

It can be reasonably expected that most proposed interchangeable products would have some design differences compared to the reference product presentation. In section VIII.B.1.b, the draft guidance provides two categories of differences in external critical design attributes: “minor design differences” vs “other design differences.”²⁸ This approach could lead to an interpretation of “other design differences” that is overly broad,²⁹ and result in unnecessary studies that do not address meaningful safety considerations. Using a prefilled syringe as an example, the task of “removing syringe needle cover” is identified as a critical task per FDA draft guidance.³⁰ This could be understood to mean the design of the needle cover would be considered an “external critical design attribute” per the definition provided in the current interchangeability draft guidance.³¹ By extension, any design differences in the needle cover, even the color, may require a comparative human factors study.

Therefore, Amgen recommends additional clarification on how to apply a risk-based approach to evaluate the differences in external critical design attributes. For example, the guidance could provide a reference to a FDA-recognized consensus standard,³² which provides an example of qualitative severity levels (catastrophic, critical, serious, minor, and negligible) as well as definitions for each level. The impact of differences in external critical design attributes could be assessed against such criteria using the use-risk analysis of the proposed interchangeable product presentation to determine if further human factors evaluation is required.

Amgen agrees with the Agency that a risk-based approach to evaluate design differences is appropriate. However, the differences in external critical design attributes should be evaluated in the context of the use-risk analysis of the proposed interchangeable product presentation alone. We do not think a direct comparison of risk profiles between a proposed interchangeable product presentation and the reference product presentation is appropriate, given that the sponsor of a proposed interchangeable product would not have the full safety information on the reference product presentation and technical knowledge about the reference product’s device design necessary to establish a risk profile for the reference product.

Section VIII.B.2 introduces the concept of a new comparative use human factors study to evaluate interchangeability and states that traditional human factors studies generally do not apply when evaluating interchangeability.³³ Amgen considers both the traditional human factors validation study and the comparative use human factors study important for the evaluation of a proposed interchangeable product for different reasons. The traditional human factors validation study is necessary to validate the safety and effectiveness of the user interface of the proposed interchangeable product presentation itself based on its iterative design development and results of formative studies. The comparative use human factors study may also be necessary to study the use risks specifically associated with switching between the reference product and the proposed interchangeable product.

In addition to traditional human factors studies, comparative human factors studies allow for direct observation of study participants performing drug administration using both the reference product and the proposed interchangeable product. Rather than collecting only subjective feedback on the reference product to establish baseline for comparison, comparative human factors studies provide context for root cause analysis on use errors observed with the proposed interchangeable product. However, human factors studies are intrinsically qualitative in nature, with emphasis on root cause analysis for use errors and risk mitigations, so a statistical approach with a noninferiority study design may not be appropriate. Importantly, since not all use errors are equal (i.e. some have higher risk than others), a direct

²⁷ FDA, Guidance for Industry and Food and Drug Administration Staff: Applying Human Factors and Usability Engineering to Medical Devices Guidance (Feb. 3 2016), at p. 2.

²⁸ FDA, Draft Guidance for Industry: Considerations in Determining Interchangeability with a Reference Product (Jan. 2017), at p. 21.

²⁹ FDA, Draft Guidance for Industry: Considerations in Determining Interchangeability with a Reference Product (Jan. 2017), at p. 21.

³⁰ FDA, Draft Guidance for Industry: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development (Feb. 2016), at p. 7.

³¹ FDA, Draft Guidance for Industry: Considerations in Determining Interchangeability with a Reference Product (Jan. 2017), at p. 21.

³² AAMI ANSI ISO 14971, ISO 14971, Medical Devices – Applications of Risk Management to Medical Devices (2007).

³³ FDA, Draft Guidance for Industry: Considerations in Determining Interchangeability with a Reference Product (Jan. 2017), at p. 22.

comparison of overall use error rates could confound the interpretation of study results. This may complicate the use of a quantitative measure to compare risk between the two devices. Therefore, Amgen recommends applying a detailed, qualitative analysis to evaluate study results from a comparative use human factors study. In these situations, FDA should consider the evaluations on a case-by-case basis.

F. “POSTMARKETING SAFETY MONITORING CONSIDERATIONS” – (Section IX of the Draft Guidance, beginning at page 23)

The draft guidance appropriately recognizes the important role that post-marketing safety monitoring must play with regard to all biologics, particularly as the marketplace increases in complexity with the arrival of biosimilars and interchangeable products. As explained in the draft guidance, “Robust post-marketing safety monitoring is an important component in ensuring the safety and effectiveness of biological products, including biosimilar and interchangeable products.”³⁴ Amgen believes that a robust pharmacovigilance system for biologics should account for both passive and active acquisition of safety signals and for different settings of use (e.g., the pharmacy benefit for self-administered biologics versus the medical benefit for physician-office administered biologics).

We have expressed our support for vigorous pharmacovigilance in our response to the FDA’s draft naming guidance,³⁵ and have also published considerations for biologic pharmacovigilance in *Biodrugs*.³⁶ Both passive and active surveillance situations are currently subject to distinct gaps in signal detection that impact the fidelity of adverse event data conveyed to FDA or the manufacturer. FDA, the Center for Medicare and Medicaid Services (CMS), and/or the U.S. Department of Health and Human Services (HHS) can influence standards and best practices to improve pharmacovigilance. With regard to interchangeable products specifically, we urge FDA to apply its policy for unique and distinguishable suffixes to help ensure that adverse events are accurately associated with the product or products received by the patient.

II. ADDITIONAL POINTS FOR CONSIDERATION

Below are additional points for consideration, as well Amgen’s response to the “Topics for Discussion” presented in the Federal Register.

A. Additional Topics to Be Considered

In addition to the considerations presented in the guidance, Amgen requests that FDA address some additional factors that are relevant to interchangeability.

1. Amgen requests FDA make clear that an interchangeability designation does not confer a relationship between two biologics, that are each designated as interchangeable to the same reference product.

The studies performed to support a designation as an interchangeable product apply only to the reference product and the biosimilar that is granted the interchangeable designation. Prescribers, patients, and industry would benefit from an explicit statement in the interchangeability final guidance, product labeling, and the “Purple Book” that the interchangeable product *alone* is substitutable for its reference product and that the interchangeability designation does not reflect any relationship with another biosimilar or with another interchangeable product to the same reference product.

³⁴ FDA, Draft Guidance for Industry: Considerations in Determining Interchangeability with a Reference Product (Jan. 2017), at p. 23.

³⁵ Amgen Comments on FDA Nonproprietary Naming of Biological Products; Draft Guidance for Industry (Oct. 2015). Available at <https://www.regulations.gov/document?D=FDA-2013-D-1543-0166>. Last accessed 14 February 2017.

³⁶ Grampp, G. and Felix, T. Pharmacovigilance Considerations for Biosimilars in the USA, *Biodrugs*, 2015; 29(5):309-321.

The elements and characteristics of chemical drugs *are* considered to be transitive once they have been declared therapeutically equivalent.³⁷ With multi-source generics, the frequent switching between generic products is a regular practice.³⁸ Given that this is the paradigm clinicians and pharmacists are most familiar with in the context of substitution, it is important that FDA policy distinguish between generics and biologics to avoid inappropriate and inadvertent substitution.

Unlike generic drugs, biosimilars and interchangeable products of the same reference product will not be supported by a demonstration of “sameness” to the reference product; rather, they will be “highly similar” to the reference product. One biosimilar product designated as interchangeable cannot be considered interchangeable to other interchangeable products simply by virtue of their independent similarity to the same reference product. Currently, FDA guidance does not require one biosimilar or interchangeable product to be compared to another biosimilar or interchangeable product. One of the primary reasons given by FDA for the approach taken in its final guidance on nonproprietary naming for biologics was that it would “help minimize inadvertent substitution.”³⁹ For the same reasons, we believe a clarification as to the meaning of an interchangeability designation awarded to a biosimilar should be clearly stated in the product label and in the “Purple Book.”⁴⁰

2. A statement of interchangeability and clinical data supporting interchangeability should be included in the product labeling and will facilitate appropriate use by healthcare professionals.

While FDA has addressed the labeling of biosimilars in its draft guidance on biosimilar labeling,⁴¹ labeling of interchangeable products was not addressed. Consistent with FDA’s recognition of the importance of including a statement of biosimilarity in the label of an approved biosimilar, Amgen urges the inclusion of a similar statement of interchangeability in product labeling for interchangeable products. This information is vitally important in aiding physicians and pharmacists in product selection, prescribing, and dispensing. As FDA notes, only biosimilars that have met the additional approval standard of interchangeability are affirmatively found to be safe for substitution with the reference product without the intervention of the prescriber.⁴² Clear labeling of a product as an interchangeable or biosimilar will provide several benefits to patients, prescribers, and pharmacists.

First, clinicians may make prescribing decisions based on the unique circumstances of a particular patient. Clarity in the label that a product is interchangeable will help inform prescriber and patient choice as well as enable safe and appropriate use. As FDA has stated, “Health care practitioners are accustomed to looking to the prescription drug labeling as their primary source of information about a product.”⁴³

Second, knowledge of an interchangeability designation is important for a pharmacist to be able to make an appropriate substitution. In the event that multiple products may be approved as either biosimilar or interchangeable with a single reference product, clarity in the label will ensure continuity of information between the prescriber and the pharmacy. Supporting this concept, surveys of 400 pharmacists and 400 physicians conducted by the Alliance for Safe Biologic Medicines (ASBM) found that over 80% of those surveyed believe it is important or very important that a product label indicate whether the biosimilar

³⁷ FDA, Therapeutic Equivalence of Generic Drugs – Letter to Health Practitioners (Jan. 1998). Available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm073182.htm>. Last accessed 14 February 2017.

³⁸ FDA, Office of Generic Drugs, Center for Drug Evaluation and Research. Facts about generic drugs. (June 2012). Available at: <http://www.fda.gov/20Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm>. Last accessed 14 February 2017.

³⁹ FDA, Guidance for Industry: Nonproprietary Naming of Biological Products (Jan. 2017), at p. 1.

⁴⁰ FDA, Purple Book, at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM439049.pdf>. Last accessed 14 February 2017.

⁴¹ FDA, Draft Guidance for Industry: Labeling for Biosimilar Products, Draft Guidance for Industry (March 2016).

⁴² 42 U.S.C. § 262(i)(3).

⁴³ 71 Fed. Reg. 3922 (Jan. 24, 2006), at 3964.

is interchangeable with the originator product.⁴⁴ These suggestions are consistent with FDA's guidance recommending the inclusion of a statement of biosimilarity "on the line immediately beneath the U.S. approval date in Highlights."⁴⁵

Lastly, the specific reference product presentation to which the biosimilar is deemed interchangeable should be clearly noted in the product label. The draft guidance suggests that a sponsor of an interchangeable product may seek an interchangeable designation with a subset of presentations offered by the reference product. In order to ensure that patients receive medications in a presentation for which they have been appropriately trained to administer, *presentation specific* information as to a product's interchangeability should be clearly specified in the label.

For example:

*[BIOSIMILAR PRODUCT'S PROPRIETARY NAME-PRESENTATION (biosimilar product's proper name/presentation specifics)] is interchangeable[†] with [REFERENCE PRODUCT'S PROPRIETARY NAME-PRESENTATION (reference product's proper name/presentation specifics)], **and only with** [REFERENCE PRODUCT'S PROPRIETARY NAME-PRESENTATION (reference product's proper name/presentation specifics)] for the indications listed.*

[†]Interchangeable means that the biological product is approved based on data demonstrating that it is biosimilar to an FDA-approved biological product, known as a reference product, can be expected to produce the same clinical effect in any given patient, and is safe to be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

This descriptive information is intended to clearly distinguish an interchangeable product and presentation from a non-interchangeable product. This distinction will help minimize confusion among prescribers regarding the definition of interchangeability in the U.S. and minimize the potential for inadvertent switching between products or pharmacy-level substitution of a non-interchangeable product.

In addition, we urge FDA to require that product labeling include a summary of the clinical data used to demonstrate interchangeability. As FDA has explained, "the approved prescribing information summarizes the essential scientific information needed by health care practitioners for the safe and effective use of a drug."⁴⁶ While it is FDA's responsibility to make decisions for the public at large, it is the prescriber's responsibility to make treatment decisions for the individual patient. Clinical switching trials used to support a demonstration of interchangeability can be used to assess the safety of switching from a reference product to an interchangeable product and therefore be useful information for health care providers making patient-specific decisions.

Clinician confidence will play a major role in advancing a robust, patient-focused biosimilar marketplace in the U.S. Providing physicians easy access to available clinical data and the source of that data via a product label fosters efficient and safe use of biologics. We therefore recommend that for all biosimilars, FDA, at a minimum, support the inclusion of a link accompanying the online version of the product label that navigates to an FDA-published version of the International Pharmaceutical Regulators Forum's (IPRF) Public Assessment Summary Information for Biosimilars (PASIB). This approach aligns with a similar proposal from FDA to create a new online labeling repository as a source of real-time information for the public.⁴⁷

⁴⁴ ASBM Labeling Survey, February 2015. Available at <https://safebiologics.org/2015/10/asbm-releases-pharmacist-survey-findings-show-strong-support-for-distinguishable-names-for-biologics-and-need-for-transparency-in-labeling/>. Last accessed 13 March 2017.

⁴⁵ FDA, Draft Guidance for Industry: Labeling for Biosimilar Products (March 2016).

⁴⁶ 21 CFR §§ 201.100 and 201.56(a)(1).

⁴⁷ In the Federal Register notification and Congressional testimony regarding the generic drug labeling rule, FDA suggested (and has already implemented) a labeling repository to publish labels which may still be under Agency review. The website, labels.fda.gov, allows health care providers and the public to gain access to important updated labeling information much sooner than would be the case if the labels had to first clear Agency review and then post on Drugs@FDA. See <https://www.federalregister.gov/articles/2013/11/13/2013-26799/supplemental-applications-proposing-labeling-changes-for-approved-drugs-and-biological-products>.

We thus urge FDA to distinguish its approach for interchangeable product labeling from that of generic drugs, both with regard to labeling format (e.g., an interchangeability statement, presentations) and content (eg, product-specific clinical data associated with biologic products designated interchangeable). Amgen respectfully requests FDA address these labeling concerns for interchangeable products in future versions of this guidance and future versions of the labeling guidance.

3. FDA guidance on nonproprietary naming for biologics should be applied in an identical manner to biosimilars and interchangeable products in order to mitigate inadvertent substitution and confusion by health care professionals.

In the recent final guidance on Nonproprietary Naming of Biologics, FDA described its approach to designating the proper name for originator and related biological products licensed under section 351(a) of the PHS Act and for biosimilar products licensed under section 351(k) of the PHS Act.⁴⁸ The document, however, did not provide framework for naming interchangeable products. Amgen requests that naming guidance for interchangeable products be provided by the Agency through an appropriate means. The distinguishable suffix described in FDA's recent final guidance would accomplish the same goal for interchangeable products as intended for biosimilars, and is thus applicable to both.

Amgen requests that the Agency apply the same nomenclature system to both biosimilars and interchangeable products. As noted by FDA, product irregularities for biologics can develop at any point in the life cycle of a product; therefore, it is essential that all biologics can be identified with specificity and associated with a distinct manufacturer, regardless of whether the biologic is a reference product, a biosimilar, or an interchangeable product. Assigning interchangeable products unique suffixes in the exact same manner as with reference products and biosimilars would minimize confusion, prevent complications with traceability, and would allow accurate attribution of adverse events. The converse would be true, however, were a reference product and an interchangeable product to share the same suffix.

4. FDA should establish an appropriate mechanism to reclassify a designation from an interchangeable to a biosimilar, should circumstances arise that warrant Agency action.

The designation of a biosimilar as interchangeable should be expected to remain in place so long as it is scientifically appropriate. However, occasions may arise when reclassification of an interchangeable product to a non-interchangeable biosimilar is necessary. FDA currently has a framework for addressing the removal of an AB rating in the generic drug paradigm; stakeholders have an opportunity to comment on a proposed change in a therapeutic equivalence rating, and the sponsor may request a hearing prior to any withdrawal of an application.⁴⁹ Sponsors of interchangeable biologics similarly should be afforded due process protections before FDA withdraws an interchangeability designation.

The possibility that an interchangeable designation may need to be withdrawn is rooted in the nature of biologics. Biological products are very sensitive to manufacturing processes, handling conditions, and environmental factors that could affect the structure and quality of the product in ways that may have clinical implications for patients. In addition, real-world use with regard to switching patients between a reference product and an interchangeable product will be very different than the controlled clinical trial environment and may bring to light unexpected outcomes. New information that provides additional insight into implications of switching may necessitate action on the part of FDA. For these reasons, Amgen believes that FDA should establish a transparent mechanism by which the Agency may reclassify an interchangeable to a biosimilar in a manner that affords the sponsor an opportunity to address FDA's concerns prior to such reclassification.

⁴⁸ FDA, Guidance for Industry: Nonproprietary Naming of Biological Products (Jan. 2017).

⁴⁹ FDA, Orange Book Preface, Section 1.9 Therapeutic Equivalence Code Change for a Drug Entity, available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm>. Last accessed 14 February 2017; 21 U.S.C. 355(e).

The current status of an interchangeability designation is relevant to the prescriber, the patient, and the pharmacist. In addition to the role of an interchangeability designation in pharmacy-level substitution, prescribers themselves may consider a designation of interchangeability in the course of choosing a biological medicine for an individual patient. Therefore, any changes to an interchangeable designation initiated by FDA should be reflected in the biosimilar product label (through a label update) and in the “Purple Book.”⁵⁰

B. Federal Register Notice Questions

FDA’s Federal Register Notice announcing the release of the draft guidance on interchangeability also included additional questions for stakeholder consideration. Amgen appreciates FDA seeking stakeholder feedback on these additional important points for consideration. Provided below are Amgen’s comments and perspectives on these matters.

1. **“With respect to interchangeable products, are there considerations in addition to comparability assessments that FDA should consider in regulating post-approval manufacturing changes of interchangeable products? Your comments should include appropriate scientific rationale and justification for your recommendations, as well as recommendations for processes and systems (including key logistics) to implement your recommendations.”**

Post-approval manufacturing changes made to reference biological products, biosimilars, and interchangeable products should be treated in a similar manner (e.g., consistent with FDA’s guidance on comparability), and once approved, each product should be managed independently.⁵¹

Updates to manufacturing processes of biologics may be necessary as a result of a range of regulatory, market, and operational factors.⁵² These factors will not necessarily impact all biologics manufacturers evenly or at the same time, which means that the manufacturing processes for an interchangeable and a reference product may be changed at different times and/or in different ways.⁵²

Due to the impact manufacturing processes can have on biologics, changes to these processes may affect product quality attributes over time.⁵³ The extent to which the variability and degree of these changes affect the relationship between a reference product and an interchangeable product is likely a very difficult situation for which to establish appropriate and scientifically-sound controls. While modern analytical techniques used in comparability studies are sensitive, there are still no current methods that can reliably predict the likelihood of a biological product to result in adverse events, including immunogenicity. This notion underscores the critical importance of appropriate naming and pharmacovigilance practices for all biologics in that robust measures for traceability facilitate accurately attributing to a specific product the unpredicted issues that may arise post-approval.

2. **“How, if at all, should the Agency consider conditions of use that are licensed for the reference product after an interchangeable has been licensed?”**

The pursuit of innovation should not be limited by policy governing biosimilars; innovation in therapeutics as well as their delivery methods has the potential to improve patient care. FDA should anticipate that the sponsor of a reference product may continue to pursue new conditions of use which could serve to

⁵⁰ FDA, Purple Book, at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM439049.pdf>. Last accessed 14 February 2017.

⁵¹ FDA, Guidance for Industry: Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information (April 2016).

⁵² Ramanan, S., and Grampp, G. Drift, evolution, and divergence in biologics and biosimilars manufacturing. *Biodrugs*, 2014; 28(4):363-372.

⁵³ Genazzani AA et al. Biosimilar drugs: concerns and opportunities. *Biodrugs*. 2007; 21(6):351-356.

benefit patients and/or means of delivering the therapeutic; this should not be discouraged, but does make maintaining a designation of interchangeability complicated.

For the reasons discussed earlier (section I.E), Amgen believes that it is in the best interest of patients that an interchangeable designation be granted and retained only when it applies to all indications available to the reference product. Under the 351(k) pathway, a biosimilar applicant may use extrapolation of indications to support licensure in conditions of use not directly studied in its clinical trial program.⁵⁴ Amgen supports the use of extrapolation when scientifically justified and when sufficient pharmacological and clinical evidence have been obtained in an appropriately sensitive patient population. Using this approach, additional indications should be addressed on a case-by-case basis. For situations in which a new indication for the reference product is protected due to intellectual property or regulatory exclusivity, FDA may consider requiring the interchangeable product sponsor, at a minimum and in a period of time decided by the Agency, to provide scientific justification that the product is appropriate for use in the new indication. This is important for patients because prescribers and pharmacists are familiar with the generic drug paradigm in which products are generally designated as AB rated for all indications; thus, prescribers may assume the same principles apply to biologics and prescribe products deemed to be interchangeable as such for any indication for which the reference product is approved, as is typically the case in the generic drug space. In many of these cases, extrapolation to other indications may be scientifically justified without additional clinical evidence. However, in cases where the justification is not straightforward, or cannot be provided, FDA should decide on the most appropriate path forward to ensure proper and safe use of the product.

Although extrapolation is a reasonable approach long-term, it is important for the success of the biosimilar industry that FDA effectively address the time between which a reference product receives a new indication and the sponsor of the interchangeable product should provide a scientific justification for extrapolation.

It is also important to consider the evolution of scientific knowledge and new understanding of, for example, a product's mechanism(s) of action, side-effect profile, or even risk/benefit profile. Should information arise after the approval of an interchangeable that calls into question the safety or efficacy of the therapeutic, it may be that additional clinical studies or post-marketing pharmacovigilance practices would be required. In these cases, the reference product, any biosimilars, and any interchangeable products should be expected to address these developments.

III. CONCLUSION

Amgen appreciates the work FDA has done to develop a scientifically sound framework for designating biosimilars as interchangeable with their reference products. The complexities of biologic medicines and the current limitations of analytical tools to evaluate these medicines present challenges for ensuring that the implementation of the interchangeability framework is scientifically sound. The policies require careful consideration as they will have long-term and far reaching implications for patients and the biosimilar industry. We respectfully request that FDA address the issues presented herein ahead of finalizing the guidance. Amgen remains committed to collaborating with the Agency in developing sound policies that account for scientific realities inherent with biologics in order to best serve the interests of patients.

⁵⁴ FDA, Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015).