SANDOZ
a Novartis company

March 22, 2016

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

RE: Nos. FDA-2015-P-4935

Dear Sir/Madam:

Sandoz respectfully submits the enclosed document in response to the Citizen's Petition authored by AbbVie and posted to the Federal Register on December 16, 2015 discussing interchangeability.

Yours sincerely,

Hillel Cohen, PhD
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Sandoz Inc., a Novartis Company
100 College Road West
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NOVARTIS

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

No. FDA-2015-P-4935

March 21, 2016

Dear Sir/Madam:

Sandoz, a Novartis company, respectfully submits this response[i] to the AbbVie Citizen Petition ("CP") to recommend the Food and Drug Administration ("FDA" or "Agency") reject the CP in its entirety.

The AbbVie CP requests FDA require the following as essential before the designation of any product as an interchangeable biologic:

1. Interchangeability be established in *each* condition of use for which the reference product is licensed, regardless of whether the applicant intends to label its product for every such condition of use;
2. Clarify that the statutory standards for establishing interchangeability differ in both kind and scope from the standard for establishing biosimilarity; and
3. Convene a Part 15 Hearing to obtain public input on the topic, and only subsequently issue guidance or regulations that address interchangeability.

We request FDA to deny the CP for the following reasons:

1. The rationale and data used as the basis of the CP are limited, misrepresented, and misleading;
2. BPCIA does not require the issuance of guidance prior to FDA reviewing and approving biosimilars and interchangeable biologics; and
3. A Part 15 Hearing will not provide any new or additional knowledge on this topic that will not be already be captured during the review and comment period following issuance of draft guidance on interchangeability.[1]

The arguments presented in AbbVie's CP are incomplete and the limited data provided is misrepresented and misleading. A more thorough review of the complete data set, including that

[1] FDA has already committed to publishing draft guidance on "Considerations in Demonstrating Interchangeability With a Reference Product" both in CY 2015, and more recently in CY 2016. See Guidance Agenda: New & Revised Draft Guidances CDER is Planning to Publish During Calendar Year 2016. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm417290.pdf (Accessed March 18, 2016).

available in the published literature, reveals that the data do not support the actions requested as detailed further in our response. Moreover, the CP does not recognize that biosimilarity is established predominantly analytically, not through clinical studies, which are used to confirm similarity, and that the statute[2] does not require clinical studies *per se* to establish interchangeability.

While Sandoz supports issuance of an FDA guidance document on interchangeability because it could provide clarity that will help sponsors develop interchangeable biologics, there is no legal requirement that the FDA must first issue a Draft Guidance before sponsors can seek approval of these products as interchangeable with their respective reference products.

As a legal and regulatory matter FDA was given authority in Biologics Price, Competition and Innovation Act (BPCIA), that was enacted on March 23rd, 2010, to consider a request for licensure of a biosimilar or an interchangeable biologic by a sponsor. The BPCIA envisioned, and specifically states, that the issuance of guidance "shall not preclude the review of, or action on, an application submitted under this subsection." In fact, such requests for approval of an interchangeable biologic could have been made at any time since the enactment of BPCIA as there is no requirement in the statute for any guidance on the subject. Indeed, as is always the case for even final guidance, it is only advisory and not legally binding on sponsors or the Agency[3]. The CPs appear to misunderstand FDA's authority and the broader regulatory role of Agency guidance.

Further, the CP does not recognize that biosimilarity is established predominantly by analytical methodology, not through clinical studies which are used to confirm similarity, and also that the statute does not require clinical studies *per se* to establish interchangeability.[4]

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[2] TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition and Innovation (BPCI Act) provisions of the Patient Protection and Affordable Care Act (PPACA), (2010) Pub.L.111-148, 124 Stat. 817. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (Accessed March 18, 2016).

[3] On all FDA draft and final guidance the following notification appears:

"This [draft] guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page."

[4] 42 U.S.C. § 262(k)(4):

''(4) SAFETY STANDARDS FOR DETERMINING INTERCHANGEABILITY.—Upon review of an application submitted under this subsection or any supplement to such application, the Secretary shall determine the biological product to be interchangeable with the reference product if the Secretary determines that the information submitted in the application (or a supplement to such application) is sufficient to show that—

''(A) the biological product—

''(i) is biosimilar to the reference product; and

''(ii) can be expected to produce the same clinical result as the reference product in any given patient; and

''(B) for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."

While FDA has the authority to hold a Part 15 Hearing, this activity should not delay the review and approval of biosimilar and interchangeable biologics.[5] A Part 15 Hearing may not be the best venue with which to obtain a comprehensive view of stakeholders' views. Public input will be better obtained through the invitation to comment on the Draft FDA guidance on interchangeability when it is issued. We believe that the CP's recommendation for a Part 15 meeting is simply part of ongoing efforts to delay the licensure and adoption of biosimilars, promote hypothetical safety concerns where none exist and to undermine the very concept that all FDA regulated biologics, including interchangeable ones, are approved only if they meet the single Public Health Safety Act standard of safety, purity and potency. Biosimilars and interchangeable biologics have the potential to add significant benefits to the US healthcare system over and above those already established by originator biologics, and efforts to create unwarranted negative perceptions or delay their availability and adoption should be rejected as inappropriate and unfair to the American consumer and their healthcare providers.

We appreciate that interchangeability for biologics represents an important topic of substantial public interest and that clarification of several key points will be useful. However, we also want to acknowledge the extensive experience[6] and regulatory leadership of FDA with comparability in support of manufacturing changes[7,8], and the inevitable relationship of those decisions, as a scientific matter, with those of biosimilarity. We recognize that as a legal matter, FDA's authority to approve biosimilar and interchangeable biologics was created in the BPCIA[9], and in the Statute it is clear that:

- Interchangeability does not represent a higher standard of safety or clinical effectiveness. All biologics approved by FDA are safe, pure and potent for their intended

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[5] FDA has already held a number of Part 15 Hearings on Biosimilars both pre- and post- enactment of BPCIA, including in September 2004, February 2005, November 2010, and May 2012. See e.g., FDA, Part 15 public hearing on approval pathway for biosimilar and interchangeable biological products November 3, 2010. Transcript available at: http://www.fda.gov/downloads/Drugs/NewsEvents/UCM289124.pdf (Accessed March 18, 2016); FDA, Center for Drug Evaluation and Research, Office of Medical Policy, Part 15 public hearing on draft guidances relating to the development of biosimilar products May 11, 2012. Transcript available at: http://www.fda.gov/downloads/Drugs/NewsEvents/UCM310764.pdf (Accessed March 18, 2016).

[6] Vezér B, Buzás Z, Sebeszta M, and Z Zrubka (2016) "Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents", *Current Medical Research and Opinion*, DOI: 10.1185/03007995.2016.1145579. Available at: http://dx.doi.org/10.1185/03007995.2016.1145579 (Accessed March 18, 2016).

[7] FDA Guidance for Industry, "Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products", April 1996. Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm (Accessed March 18, 2016).

[8] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline: "Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process Q5E," November 18, 2004. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (Accessed March 18, 2016).

[9] TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition and Innovation (BPCI Act) provisions of the Patient Protection and Affordable Care Act (PPACA), (2010) Pub.L.111-148, 124 Stat. 817. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (Accessed March 18, 2016).

use,[10] and consequently interchangeability is a requirement for additional data, not a different standard, and that

- Interchangeable biologics and biosimilars must be manufactured to the same quality levels as are applied to originator biologics.[11]

I. Interchangeability: What it is and what it is not

The concept of interchangeability is a unique new category for biologics created in the BPCIA. As a pre-requisite to be considered as an interchangeable biologic, a given biological drug must first be determined to be biosimilar to a US-licensed reference product (approved under 351(a) of PHS Act[12]). Both designations, biosimilar and interchangeable biologic, are based on the totality of the evidence presented by the 351(k) product sponsor. To obtain an interchangeability designation from FDA evidence must be provided to establish that the biosimilar *can be expected* to produce the same clinical result as the reference product in any given patient;" and "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."[13]

The wording in the BPCIA describing the requirements for interchangeability is consistent with established regulatory pathways for drugs, biologics and devices that the pre-approval studies establish an *expectation* for how the product will behave in future patients. It is also very specific in that the evidence provided by the sponsor establishes an *expectation* that the biosimilar produces the same clinical effect in any given patient.

As the FDA and other health authorities have made clear, the clinical performance of biosimilars and interchangeable biologics is rooted in the analytical and functional comparisons which demonstrate that the biosimilar is "highly similar,"[14] or as stated succinctly and simply by the EMA, it is "essentially the same" drug substance as the reference product.[15] If it is the highly similar/essentially the same drug substance that is subsequently confirmed by the clinical trial to

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[10] 42 U.S.C. §262 (a)(2)(c)(i)(I): "the biological product that is the subject of the application is safe, pure, and potent".

[11] FDA Guidance for Industry, "Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product", April 2015. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291134.pdf (Accessed March 18, 2016).

[12] 42 U.S.C. §262(a).

[13] 42 U.S.C. § 262(k)(4).

[14] FDA's Overview of the Regulatory Guidance for the Development and Approval of Biosimilar Products in the US. Available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM428732.pdf (accessed March 21, 2016)

[15] European Medicines Agency, "Questions and answers on biosimilar medicines (similar biological medicinal products)", September 27, 2012. EMA.837805/2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf (accessed March 18, 2016).

behave in the same manner, then as a matter of science and medicine it is necessarily expected to perform the same as the reference product in any given patient in the future. That is indeed the purpose of any clinical study for any drug or biologic. And all such products are then determined to be safe and effective by the FDA, indeed this is intrinsic to their approval.

It is evident that interchangeability is a requirement for additional data and does NOT represent a higher approval standard for the product itself. To suggest otherwise would imply that biosimilars are LESS safe and less effective than interchangeable biologics – clearly an inappropriate conclusion since the product itself is the same.[16] Further, interchangeable biologics and biosimilars must be manufactured to the same quality levels[17] as are applied to all other originator biologics. Irrespective of the regulatory development and approval pathway, the manufacturing, control and product quality standards are the same for all biologics approved in the U.S. In addition, the facilities are always inspected and licensed by the FDA, and the standards for biosimilar and interchangeable biologics manufacturing establishments are the same as those applied to facilities used in manufacture of reference products.

The concept of interchangeability has no bearing on the ability of a prescribing physician to select the best therapy for a given patient. Instead, it applies to the practice of pharmacy because a biosimilar that is deemed to be interchangeable with its reference product can be substituted by a pharmacist for its reference product without the intervention of the healthcare provider that provided the original prescription. Namely, interchangeability is defined in BPCIA as follows:

> *"The term 'interchangeable' or 'interchangeability', in reference to a biological product that is shown to meet the standards described in subsection (k)(4), means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product*."[18]

A prescriber can always specify the specific product to be prescribed and check the "do not substitute" or "dispense as written" box on the prescription pad, just as is that case for any other drug or biologic in the United States. As such the prescriber continues to have control over the actual product received by the patient, even when an interchangeable drug (listed in the Orange Book[19]) or interchangeable biologic (listed in the Purple Book[20]) is available.

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[16] McCamish M, Pakulski J, Sattler C, and G Woollett, "Toward interchangeable biologics," *Clinical Pharmacology & Therapeutics*, 97(3):215-17 (March 2015). Available at: http://onlinelibrary.wiley.com/doi/10.1002/cpt.39/pdf (Accessed March 18, 2016).

[17] FDA Guidance for Industry, "Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product", April 2015. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291134.pdf (Accessed March 18, 2016).

[18] 42 U.S.C. § 262(i)(3).

[19] FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (The Orange Book), 36th Edition (2016). Available at: http://www.fda.gov/downloads/drugs/developmentapprovalprocess/ucm071436.pdf (Accessed March 18, 2016).

[20] FDA's "Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations," last updated Feb. 29, 2016. Available at:

Meanwhile, as a regulatory matter, since 1996, FDA has used "comparability" as the *de facto* interchangeability standard for all biological medicines that are subjected to manufacturing process changes.[21] These biologics include those products used as reference products for current and future biosimilars and interchangeable biologics. Such changes, including implementing more modern technologies, scaling up the process to make more product or transferring the manufacturing process to other facilities, commonly results in changes to the molecular structure of the biological medicine.[22, 23] Regulatory authorities must review and approve all such changes prior to using products from this new process in patients. Comparability has a very good safety record, and the biologics pre and post manufacturing changes behave in essentially the same manner clinically. A recent report highlights that of 29 monoclonal antibodies marketed in Europe for which 404 manufacturing changes were made, 22 of the manufacturing changes were categorized as high risk and 286 as moderate risk.[24] Most of these monoclonal antibodies are also marketed in the U.S. and were likely subjected to the same manufacturing changes. It is interesting that in the U.S., transparency with physicians, healthcare personnel and patients is completely lacking with regard to these manufacturing changes as the decision to support approval of products made by a modified manufacturing process is not publicly disclosed in the U.S. (such information is available in European Public Assessment Reports provided in the EU by the EMA, and analytically the matches maintained between EU and US biologics is evidence that similar changes are occurring concurrently in both jurisdictions,[25] and likely elsewhere). This lack of transparency has not been of concern to the public or healthcare community, although it is increasingly apparent that many healthcare providers do express concern when they hear of some of the changes subsequently. Then educational efforts are required to explain that these manufacturing changes are appropriate

http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm (Accessed March 18, 2016).

[21] FDA Draft Guidance: "ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process, Nov. 13, 2003. Available at: http://www.fda.gov/OHRMS/DOCKETS/98fr/2004d-0118-gdl0001.pdf (Accessed March 18, 2016) defines "comparable" as:

> "A conclusion that products are highly similar before and after manufacturing process changes and that no adverse impact on the quality, safety or efficacy of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might be indicated."

[22] C Schneider. "Biosimilars in rheumatology: The winds of change." *Ann Rheum Dis* (2013) 72(3): 315-318. This article provides examples from the EU, but analytically similar changes can be seen concurrently in the same products markets in the US. However, the use of comparability to support manufacturing changes is not public in the US.

[23] Vezér B, Buzás Z, Sebeszta M, and Z Zrubka (2016) "Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents", *Current Medical Research and Opinion*, DOI: 10.1185/03007995.2016.1145579. Available at: http://dx.doi.org/10.1185/03007995.2016.1145579 (Accessed March 18, 2016).

[24] Vezér B, Buzás Z, Sebeszta M, and Z Zrubka (2016) "Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents", *Current Medical Research and Opinion*, DOI: 10.1185/03007995.2016.1145579. Available at: http://dx.doi.org/10.1185/03007995.2016.1145579 (Accessed March 18, 2016). In the EU, EMA publishes public assessment reports of their analysis of post-approval changes as well a summary of the data analyses leading to initial approval.

[25] Schiestl M, Stangler T, Torella C, Cepeljnik T, Toll H, and R. Grau. (April 2011) "Acceptable Changes in Quality Attributes of Gylcosylated Biopharmaceuticals", *Nature Biotechnology*, 29(4):310-312.

and adequately regulated by FDA, and the safety and efficacy of the biologics in question has been fully maintained.

Since new lots of biological medicines made with a revised process will be introduced into the market prior to the shelf-life expiration of lots made with a prior process, often patients will be switched from the "old" product to the "new" product during their course of treatment regardless of the indication being treated, or the preference of either physicians or pharmacists. This interchange occurs without prior notice of any healthcare worker simply because there has been a regulatory judgement that the old and new products are essentially the same or "highly similar"[26]. In this case, the sponsor has to document "comparability" by demonstrating the new product is "highly similar" to the old product. In most cases, comparability is established by use of analytical comparability protocols alone, a well-established regulatory mechanism that relies on the same concept of critical quality attributes that are applied to development of biosimilars.[27] Clinical trials are rarely required[28], and we are not aware of multi-cycle switching studies ever having been required. In these circumstances the product label is unchanged. There is no additional requirement or higher hurdle for the product made with the new process that is going to be automatically interchanged for the old product at the pharmacy. While the scientific issues are the same, the interchangeability designation was created in BPCIA as a legal matter that is now open to interpretation by FDA.

As is already applied with manufacturing process changes, understanding the molecule and the clinical impact of structural and functional features is central to the concept of "critical quality attributes" that allows manufacturers and the FDA to develop and control biosimilars and interchangeable biologics.[29] The experience of regulators and biologic sponsors is extensive,

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[26] FDA Draft Guidance: "ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process, Nov. 13, 2003. Available at: http://www.fda.gov/OHRMS/DOCKETS/98fr/2004d-0118-gdl0001.pdf (Accessed March 18, 2016), defines "comparable" as:

> "A conclusion that products are highly similar before and after manufacturing process changes and that no adverse impact on the quality, safety or efficacy of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might be indicated."

[27] FDA Draft Guidance for Industry: "Comparability Protocols – Chemistry, Manufacturing and Controls Information," February 2003. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070545.pdf (Accessed March 18, 2016).

[28] Testimony and answers to questions by Dr. Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer, Food and Drug Administration before the Subcommittee on Health, House Committee on Energy and Commerce May 2, 2007. Testimony available at http://www.fda.gov/NewsEvents/Testimony/ucm154017.htm (accessed March 18, 2016). In the Q&A she observed that less than 1/50-1/100 times are any clinical studies required at all when manufacturing changes are made using comparability. In addition, we are not aware of any switching studies between the pre- and post-change biologics having ever been required.

[29] FDA Guidance for Industry, "Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product", April 2015. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291134.pdf (Accessed March 18, 2016); FDA Guidance for Industry, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product", April 2015. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf (Accessed March 18, 2016); L Christl. "Overview of the Regulatory Pathway and FDA's Guidance for the Development and Approval of Biosimilar Products in the U.S", Presentation at FDA's Arthritis Advisory Committee

and in that very expertise is grounded the confidence that Congress recognized when they gave the FDA the authority to determine whether a biosimilar can be designated as interchangeable with its reference.

While the FDA will designate biologic interchangeability and list it as such in the Purple Book,[30] U.S. states regulate the practice of pharmacy, and this includes enacting laws describing how and when a pharmacist can substitute one drug for another. Initial state substitution laws were written based on the Federal Law of Hatch Waxman in 1984 that gave FDA the authority to approve generic drugs[31]. The laws in each state now need to be updated to permit pharmacy substitution of an interchangeable biologic for a reference product and vice versa. Many states have either passed or are considering the needed legislation in anticipation of the FDA approving biosimilars and designating at least some of them as interchangeable biologics.

As mentioned above, the FDA has approved manufacturing changes of varying degrees of complexity to existing biological drugs (each approved a ”standalone” original biologics under the 351(a) pathway), and has permitted the biological drugs products manufactured with the approved change to be freely interchanged with the biologic produced prior to the introduction of the manufacturing change. With this understanding, it is clear that the additional evidentiary hurdle required for a biosimilar to achieve a designation of interchangeability is based on regulatory requirements that were incorporated into the BPCIA, and are not based on scientific considerations or clinical experience with the equally complex reference biologics.

II. A sizeable body of scientific evidence already exists to support interchangeability

In their CP AbbVie claims that there is little evidence to support interchangeability and that “*the few studies that assess switching from a reference product to a biosimilar to date are limited in size, number of switches*.” This assertion is far from the truth. In 2012, Ebbers et al (2012) documented 58 clinical studies in peer-reviewed journals that together enrolled more than 12,000 subjects that evaluated switching between five biosimilar drugs and their respective reference products.[32] Since publication of that article there have been several additional peer-reviewed publications.[33] (These do not include abstracts that also discuss additional switching

meeting, February 9, 2016. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm486171.pdf (Accessed March 18, 2016).

[30] FDA’s “Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations,” last updated Feb. 29, 2016. Available at: http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm (Accessed March 18, 2016).

[31] The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417 (the Hatch-Waxman Amendments).

[32] Ebbers HC, Muenzberg M and H Schellekens. (2012) “The Safety of Switching Between Therapeutic Proteins”. *Expert Opin Biol Ther* 12(11): 1473-1485.

[33] Flodmark C, Lilja K, Woehling H and K Jarvholm. (2013) “Switching From Originator to Biosimilar Human Growth Hormone Using Dialogue Teamwork: Single-Center Experience from Sweden”. *Biol. Ther.* 3:35-43; Rashid N, Saenger P, Wu Y-L, Woehling H, Frankel M, Lifshitz F, Muenzberg M, and R Rappaport. (2014) “Switching to

studies[34]) While each individual study can be assessed and possibly criticized on study design grounds, one cannot ignore that every single peer-reviewed journal article has, without exception, concluded that the process of interchangeability poses no concerns with respect to safety and effectiveness.

In addition to peer-reviewed journal articles, there is extensive population-based experience from switching of products that are structurally similar but that are never directly compared in head-to-head studies (e.g. somatropins in Denmark, epoetins in Italy).[35] Indeed such switches are part of the normal practice of medicine and an inevitable consequence of the changing commercial environment since multi-source biologics[36] became available in Europe and elsewhere. The act of switching has not shown any pattern of safety concerns. Switches also occur as part of prescription drug management by payors and plans, and as a result of patients' changing access to care (such as through changes in employment or insurance plans, especially common in the US) – likewise no safety signals have been generated by the act of switching.

Likewise, as has been discussed in greater detail elsewhere, the originator reference products have likewise varied over time, both batch to batch, and through manufacturing changes, and similarly offer a compelling safety and efficacy record over considerable lengths of time.

Omnitrope® from Other Recombinant Human Growth Hormone Therapies: A Retrospective Study in an Integrated Healthcare System". *Biol. Ther.* 4(1-2):27-39. Erratum to: Biol Ther 4(1-2):81, DOI 10.1007/s13554-014-0017-1

[34] At least five abstracts and posters have been presented in recent years on switching of biosimilars, but they have not yet been published in the peer reviewed literature. These include a study supporting interchangeability of infliximab biosimilars in Italy (n=197) (G Fiorino et al. Prospective observational study on safety and efficacy of infliximab biosimilar in patients with inflammatory bowel disease: preliminary results of the PROSIT-BIO cohort. Presented at the Italian Group for the Study of IBD (IG-IBD), VII National Congress, Palermo, Italy); results from a real-world study of 39 patients switched from Remicade® to biosimilar infliximab (T Sokka and H Kautiainen. Poster SAT1074 Clinical experience with infliximab biosimilar – Switch from Remicade. presented at EULAR 2015, published in Annals of Rheum Dis (2015) 74:717); an abstract from the ECCO meeting from Ireland suggesting increased safety concerns when switching from Remicade® to Remsima®/Inflectra® (n=36) (C Murphy, K Sugrue, G Mohamad, J McCarth and M Buckley. Poster 505 - Biosimilar but not the same. 10th Congress of the European Crohn's and Colitis Organisation, 2015) and a two year extension (PLANETAS) of patients switched from Remicade® to Remima®/Inflectra® versus patients maintained on Remicade® (n=174) that supports maintenance of safety and efficacy (W Park et al. Efficacy and safety of CT-P13 (infliximab biosimilar) over two years in patients with ankylosing spondylitis: Comparison between continuing with CT-P13 and switching from infliximab to CT-P13, Abstract L15, presented at the 2013 ACR Annual Meeting). While Sandoz acknowledges these abstracts, we do not believe that an abstract rises to the same level of evidence as a peer-reviewed journal publication.

[35] S. Madsen Norwegian Medicines Agency. Biosimilars and Follow-on Biologics 2015 Americas, February 2015; D'Amore C, Da Cas R, Rossi M and G Traversa. (2016) "Switching Between Epoetins: A Practice in Support of Biosimilar Use." *BioDrugs* 30(1):27-32.

[36] We are using the term "multi-source biologic" to mean a biological product sharing the same international nonproprietary name with other biological products that are made by different companies in different facilities, and that are licensed via separate Marketing Authorization Applications.

III. Immunogenicity

It is important to put immunogenicity of biological drugs into perspective based on decades of use with these products. We now know that the clinical impact of anti-drug antibodies to biological drugs is most commonly low – if it were otherwise these agents would not have had the transformative impact on pharmaceutical medicine that has made them the drugs of choice for many conditions. We also know that there are profound differences in rates and levels of anti-drug antibodies elicited between different biological drugs.[37] And even when anti-drug antibodies are detected in a high percentage of biological drug recipients, the actual titer of such antibodies varies and is often low and without clinical impact. Importantly, while anti-drug antibody formation may be common with use of biologic drugs, neutralizing antibody formation that impacts clinical efficacy is less common.

To further put immunogenicity of biological drugs into perspective, the greatest risk of immunogenicity is related to the inherent protein backbone of the protein – namely, its primary, secondary and tertiary structure. This risk is first encountered when the reference product is launched and is used widely. By the time that a biosimilar or interchangeable biologic is developed to the reference product sponsors as well as the regulatory authorities already have a clear picture of the immunogenicity related to the protein structure. By definition, a biosimilar or interchangeable biologic must have an identical protein backbone. Any residual risk of immunogenicity of a biosimilar or interchangeable biologic could only be due to different post-translational modifications or a different impurity profile. While not negating this risk, it is certainly lower than the risk posed by potential immunogenicity inherent in the protein backbone, and always greater for an innovative new biologic product than for a biosimilar.

Nonetheless, it is certainly true that when present, individual immunological responses to therapeutic proteins can have very significant clinical implications. The most important concerns related to immunogenicity are:

1. Neutralizing antibodies that bind to the active site of the drug, thereby impacting efficacy
2. Neutralizing antibodies that interact with endogenous proteins
3. Antibodies that impact pharmacokinetics by altering clearance in some manner, which in turn may impact efficacy or safety.
4. Although some antibody responses to therapeutic protein products may have no apparent effect on clinical safety or efficacy, they may promote the generation of neutralizing antibodies via the mechanism of epitope spreading of antibody responses.[38]

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[37] van Schouwenburg P, Rispens T and G Wolbink. (2013) “Immunogenicity of Anti-TNF Biologic Therapies for Rheumatoid Arthritis”. *Nat Rev Rheumatol.* 9:164-172.

[38] Disis M, Goodell V, Schiffman K, and K Knutson. (2004) "Humoral Epitope-Spreading Following Immunization with a HER-2/neu Peptide Based Vaccine in Cancer Patients." *J Clin Immunol* 24(5):571-578; Hintermann E, Holdener M, Bayer M, Loges S, Pfeilschifter J, Granier C, Manns M, and U Christen. (2011) "Epitope Spreading of the Anti-CYP2D6 Antibody Response in Patients with Autoimmune Hepatitis and in the CYP2D6 Mouse Model." *J Autoimmun* 37(3):242-253.

At times, antibody formation may be stimulated by aggregation of the active moiety in a biological product. However, this is due to inadequate stability of the biologic in solution, and not to the structure of the molecule. Of note, aggregation is now routinely assessed for all biologics analytically throughout development, manufacturing and storage stability.

Combined, these concerns highlight the need to monitor the safety of ALL biologics carefully and consistently, and not just biosimilars or interchangeable biologics. This is why all biologics must be manufactured under current good manufacturing practices (cGMP)[39]. But such quality requirements should not be confused with the highly similar analytical standard fundamental to the initial approval of biosimilars and interchangeable biologics.

AbbVie and others claim that that the act of switching may trigger immunogenic events. However the argument that immunogenicity is a reason to be fearful of interchangeability does not withstand scrutiny. There is no published data to lead to a conclusion that the act of switching from one product to another increases a risk of an adverse event (AE) due to immunogenicity. Indeed there is no scientifically sound mechanism that provides an immunological basis for presupposing that the act of switching between related products would create a problem.

When one examines the existing data in interchangeability (see section above) it becomes apparent that safety issues related to immunogenicity when switching occurs are purely a hypothetical concern. None of the more than 60 clinical trial reports or surveillance data that have been published detected an increase in clinically relevant immunogenicity. In addition, routine periodic safety update reports generated with use of biosimilars in Europe over the past decade have never shown an increase in immunogenicity even when entire populations are repeatedly switched between biosimilars and their corresponding reference products as occurs in some tender markets, in particular. While we appreciate that absence of evidence is not evidence of absence, the completed clinical switching studies and the post-marketing pharmacovigilance ARE concrete evidence, and support the safety of switching between a reference product and corresponding biosimilar.

In addition, some sponsors have now generated data with pre-planned multiple switching between a reference product and the proposed biosimilar.[40] Other sponsors have conducted single switch studies ("transitions") with results that have been made public.[41] While we appreciate that the FDA has not yet reviewed and reached conclusions regarding these studies,

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[39] 21 C.F.R. § 210 Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs; 21 C.F.R. § 211 Current good manufacturing practice for finished pharmaceuticals.

[40] Blackwell K, Semiglazov V, Gascon P, Nakov R, Kramer S, Schwebig A and N Harbeck. (2014) "A Comparison of Proposed Biosimilar and Originator Filgrastim for the Prevention of Neutropenia in Patients with Breast Cancer Receiving Myelosuppressive Adjuvant or Neoadjuvant Chemotherapy: Phase III, Randomized, Double-Blind Trial (The PIONEER study)." *Blood* 124(1). Abstract presented at the 56th Annual Meeting of the American Society for Hematology.

[41] Soka T and H Kautiainen. "Clinical Experience with biosimilar infliximab." (2015) *Ann Rheum Dis* 74:17. Poster SAT0174, presented at EULAR 2015; Amgen press release, October 8, 2014. "Amgen Announces Positive Top-Line Results From Phase 3 Study Evaluating The Efficacy And Safety Of Biosimilar Candidate ABP 501 Compared With Adalimumab In Patients With Moderate-To-Severe Plaque Psoriasis". Available at: http://investors.amgen.com/phoenix.zhtml?c=61656&p=irol-newsArticle&ID=1975377 (Accessed March 18, 2016).

it is very likely that they were all conducted under the supervision of independent data monitoring committees who did not detect safety signals that would have led to the termination of those studies.

In their CP, AbbVie also makes numerous statements regarding risks related to immunogenicity that apply equally to all biologics, including originators (e.g. *Immunogenicity can thus eliminate treatment options for patients*" and "*immunogenicity can vary from patient to patient, from population to population, and from indication to indication.").* The approval process for all originator biologics entails a balance between benefit and risk, and the theoretical concerns related to immunogenicity of biological drugs are addressed via post-marketing safety surveillance which is used to monitor originator biologics and biosimilars equally.

Taken as a whole, while the specter of increased immunogenicity is indeed fearful and has resonated with many stakeholders, as a scientific matter it is utterly unwarranted. Raising serious hypothetical concerns without any supportive scientific evidence is a dangerous and irresponsible use of the Precautionary Principle[42].

IV. Sameness

In their CP, AbbVie states that "one biological product cannot be "the same" as another." AbbVie does not appreciate that the underlying principle of biosimilarity and interchangeable biologics is that there is no clinically meaningful difference between these biologics and their reference products.[43] This is a regulatory concept shared between biosimilars, interchangeable biologics and generic drugs. Each of these classes of drugs has a reference product. As a regulatory concept, "sameness" does not imply identity; rather. sameness implies that there is an expectation that there will be no clinically relevant differences seen when using one drug or the other. The degree to which identity (showing that one product is identical to the other) to the reference product can be established varies, based on the exactness with which a product can be structurally and reproducibly copied. Making an identical copy is feasible with small molecule drugs that are chemically synthesized, but this is not the case with many biologics. Molecular heterogeneity of several quality attributes of biologics always exists within the same batch and are controlled by means of process controls and product specifications In addition and very importantly, heterogeneity always exists from one batch of a biologic to the next, even if the manufacturing process is identical. Heterogenity is monitored via in-process and final product quality control testing to help ensure the same clinical outcomes when the products are used.[44]

[42] The Precautionary Principle is well defined and discussed at: http://www.precautionaryprinciple.eu/ (Accessed March 18, 2016).

[43] FDA Guidance for Industry, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product", April 2015. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf (Accessed March 18, 2016).

[44] Schiestl M, Stangler T, Torella C, Cepeljnik T, Toll H, and R. Grau. (April 2011) "Acceptable Changes in Quality Attributes of Gylcosylated Biopharmaceuticals", *Nature Biotechnology*, 29(4):310-312.

The fact that a biological drug is made in a living system does not negate the ability to engineer a product that matches the reference product in clinical performance. This has been amply demonstrated for many years when one compares the different somatropins and insulins that are already approved and marketed in the U.S. (biologics in science even as they are regulated as drugs for historical reasons[45]). There are multiple versions of each that are marketed by different companies Also, enoxaparin (derived from biological sources) and glatiramer acetate are highly complex molecules that are regulated in the U.S as drugs. Their active pharmaceutical ingredients contain a distribution of molecules of varying lengths. For many years, their complexity precluded complete analysis and attempts to engineer generic copies. However analytical science, manufacturing capabilities, and regulatory science have now progressed to the point where the FDA has recently approved generic copies of both of those molecules.[46, 47] The approved generics to the US reference products are considered the "same", indeed identical as a legal matter.

The variability observed and quantified with multiple lots of reference product provides a range of results for product attributes that are known to produce the same clinical effect. Consequently, regulators have considered such variability as NOT clinically relevant. This variability provides an acceptable range for critical quality attributes for which the biosimilar or interchangeable biosimilar must match the reference product. In manufacturing a biosimilar or interchangeable biologic, the critical quality attributes judged as important by regulators must be contained within the variation of that reference product that was already established as acceptable in commercial batches of that reference product.

The concept of critical quality attributes is central to the regulatory approach taken to assure "no clinically meaningful differences," a concept that is ignored within the AbbVie CP. There are quality attributes or molecular attributes that do not contribute to clinical performance, pharmacokinetics, or safety of the product so variability of these quality attributes is not a source of concern. This can be seen for example in another anti-TNF biologic, Enbrel® (etanercept)[48], wherein a specific glycosylation decreased from 50% enrichment to 30% enrichment with a manufacturing change, but this large difference was not judged as concerning.[49] This specific glycosylation would not be considered a "critical" quality attribute. Different quality attributes can vary in clinical impact, ranging from some being critical to the other extreme whereby a given quality attribute may have no impact on safety or efficacy at all. Contrary to the assertion of AbbVie, there is no scientific need or regulatory requirement for a biosimilar or interchangeable biologic to exactly match the range of a quality attribute that is known not to impact safety or

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[45] McCamish M, Gallager A and J Orloff. "Biosimilar by Name and Biosimilar by Nature." *The RPM Report*, July/August 2013, pp 1-8.

[46] FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (The Orange Book), 36th Edition (2016). Available at: http://www.fda.gov/downloads/drugs/developmentapprovalprocess/ucm071436.pdf (Accessed March 18, 2016). See page 3-136, listing Sandoz's enoxaparin (ANDA July 23, 2010) as A rated, Amphastar's enoxaparin (ANDA September 19, 2011) as A rated, and Teva's enoxaparin (ANDA June 23, 2014) as A rated.

[47] Sandoz's Glatopa® (glatiramer acetate) ANDA approval letter, April 16, 2015, available at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/090218Orig1s000ltr.pdf (accessed March 18, 2016).

[48] Enbrel® is a registered trademark of the Immunex Corporation.

[49] Schiestl M, Stangler T, Torella C, Cepeljnik T, Toll H, and R. Grau. (April 2011) "Acceptable Changes in Quality Attributes of Gylcosylated Biopharmaceuticals", *Nature Biotechnology*, 29(4):310-312.

effectiveness. Fortunately this is also well demonstrated with actual data, such as that obtained through manufacturing changes, the vast majority of which are well controlled and have had no impact on the safety and efficacy of the biologic concerned. For a non-critical quality attribute, variation observed outside the range seen in the reference product over time would be acceptable just as with a manufacturing change that leads to a change in a product quality attribute that is known not to be critical to safety or efficacy.

V. Extrapolation applies to interchangeability just as it applies to biosimilarity

The argument presented by AbbVie that the FDA cannot approve a biosimilar as interchangeable unless it is explicitly tested and is found to be interchangeable for every indication of use for which the reference is licensed, regardless of the indications that the interchangeable biosimilar is seeking is baffling. This argument reflects a fundamental failure to understand the core concept of biosimilarity. The whole point of showing that the active moieties in the biosimilar are highly similar to those in the reference product is that the products must therefore behave in the same way in a clinical setting. In this sense the premise of generics and of biosimilarity are the same – the only difference being the regulatory construct for biosimilarity having been established by a totality of evidence approach that includes comparability testing , whereas generics are based on therapeutic equivalence (comprising pharmaceutical equivalence and bioequivalence). In both cases, there is a scientific and regulatory principle encompassing extrapolation between indications, as well as interchangeability, even though the provisions for extrapolation and interchangeability are entirely separate in BPCIA, and not linked at all as a matter of law. In short, the "same" molecule must do the "same" thing, just as they do after manufacturing process changes.

The statutory requirement for interchangeability is: "*a biological product can be deemed interchangeable only if it can be expected to produce the same clinical result as the reference product in any patient for whom the reference product is specified."* There is no requirement in the statute that the evidence for interchangeability for each indication be obtained from a distinct clinical study. Instead, it is entirely reasonable to obtain evidence supporting interchangeability via scientifically valid extrapolation in a manner completely analogous to the use of extrapolation at the time of initial approval of a given product as a biosimilar. It is the "*expectation*" that the product produce the same clinical effect and that expectation is built on the data demonstrating "sameness" (often including a clinical trial in one indication to reduce residual uncertainty, but not to re-establish safety and efficacy for the biosimilar even in that one indication). Very simply, the science of "sameness" of extrapolation as it relates to biosimilarity or for interchangeability are themselves identical. The FDA reviews requests for extrapolation of every indication on a case-by-case basis, based on the totality of evidence provided by the sponsor that considers

the analytic similarity or "sameness" of the molecule combined with the mechanism of action (when known), as well as what is known about the biologic in the setting of each indication.[50]

Since a biologic must first be approved as a biosimilar before it can be considered to be interchangeable, pharmacists can have the same confidence in the FDA findings of safety, purity and potency for an extrapolated indication of an interchangeable biologic that prescribing physicians will have for extrapolated indications of a biosimilar.

In a section entitled "*Post Interchangeability Determination Product Changes*" AbbVie acknowledges that there is no need to reestablish interchangeability for new indications that are obtained after initial approval as an interchangeable biologic unless there is a known scientific concern to believe that interchangeability of the new indication may be problematic. The very same argument that AbbVie presents with respect to the interchangeability of post-approval new indications is equally valid for extrapolation of interchangeability in pre-approval settings. There is no valid reason to assume that interchangeability indications cannot be extrapolated unless there is a known scientific concern.

To conduct studies in indications that one does not seek approval for is illogical, provides no additional scientific or clinical value and is contrary to the principle of extrapolation. Such a request is contrary to the purpose of the BPCIA of providing for an abbreviated pathway in which the basis for totality of evidence are analytical and nonclinical comparisons to the reference product, followed by PK and PD studies in healthy individuals, with clinical studies in disease populations conducted only to confirm the high similarity already established in a step-wise manner with these prior comparative studies. The request made by AbbVie is clearly and unambiguously an attempt to increase the barriers to development of biosimilars and interchangeable biologics that would in turn limit competition to their biologic products on which exclusivity has expired and dossiers for potential biosimilar competitors accepted for review by FDA.[51]

VI. Indications of use

Sandoz agrees that an interchangeable biologic may not be labeled for all of the same indications as the reference product due to patent or exclusivity reasons, even if is highly similar in all parameters evaluated, including analytical, function, nonclinical, PK/PD studies and a sensitive clinical safety and efficacy study(ies). That is because, even if it is scientifically

[50] AbbVie uses several citations to argue that "any" given patient means "all" patients, however such arguments are completely contrary to such references. In one cited case (*Ali v. Fed. Bureau of Prisons*, 552 U.S. 214 (2008) the Supreme Court determined that "any" has an expansive meaning that is "one or some indiscriminately of whatever kind." The Webster's definition is similar and adds "one or another taken at random." These references actually support an interpretation that "any given patient" means any random but specific patient. "Any" and "all" do not have the same meaning and to argue that they do is completely illogical.

[51] Amgen press release, November 25, 2015. "Amgen's First Biosimilar Biologics License Application For ABP 501 Submitted To U.S. Food And Drug Administration". Available at: http://www.amgen.com/media/news-releases/2015/11/amgens-first-biosimilar-biologics-license-application-for-abp-501-submitted-to-us-food-and-drug-administration/ (Accessed March 18, 2016).

indistinguishable there may be regulatory or patent-related constraints on FDA's ability to grant a complete label. And there is no concern should this be the case – after all that is why such care is taken with the accuracy and wording of the label. Despite a legitimately less that complete label, perhaps absent some indications, AbbVie is requesting that a sponsor seeking interchangeability conduct clinical studies in these additional indications. It is unethical to conduct clinical experiments under conditions for study participants who will not be able to access a drug after study completion and hence be unable to benefit by use of the drug[52].

AbbVie presupposes that physicians and pharmacists will assume that an interchangeable biologic will be interchangeable for all indications of the reference product. This contention by AbbVie is not substantiated. Pharmacists will be able to review in the Purple Book whether a given biologic is a biosimilar or interchangeable biologic. And as with any other drug, pharmacists have a professional obligation to understand the product label and the prescribers' instructions.

Physicians are always free to select the most appropriate individual therapy for their patients, and this may include an indication not on the label of the biosimilar or reference product. This is the very purpose, but also the limitation, of the label and FDA role in the practice of medicine. The indications granted to all drugs, irrespective of their approval pathway, are very clearly listed within the Product Information, in both the Summary at the beginning of the Product Information as well as in the body of the Product Information itself. These are available to the prescriber to use in the context of his best judgement as to the needs of his particular patient.

VII. Historical arguments

The historical argument presented by AbbVie is inherently and critically flawed. Statements made and positions articulated in early drafts of guidances and legislation but not present in later drafts were intentionally discarded by their authors, and either no longer reflect current science or current regulatory policy. Without going into a point by point rebuttal it is self-evident that statements and positions that were discarded cannot be used to support current arguments in support of a desired policy position, let alone invoke the support of those authors who have already revised their opinions and expressed them in statutes and regulatory guidance.

Conclusions

The FDA should reject the AbbVie request to require sponsors seeking interchangeability to conduct clinical studies in all indications for which the reference product is approved, including those for which the biosimilar is not indicated for the following reasons:

[52] See PhRMA "Principles on the Conduct of Clinical Trials; Communication of Clinical Trials Results". Available at: http://phrma.org/sites/default/files/pdf/042009_clinical_trial_principles_final_0.pdf (Accessed March 18, 2016).

- Ample scientific evidence is available supporting the fact that the act of switching between a biosimilar and its corresponding reference product does not by itself raise concerns.
- The specter of increased immunogenicity due to the act of switching is purely hypothetical and is not supported by any existing scientific evidence.
- The concept of data extrapolation extends to the concept of interchangeability just as it applies to the initial assessment of biosimilarity.
- It is unethical to conduct clinical studies in indications protected by patent or exclusivity reasons because study participants cannot expect to benefit by continued use of the drug after conclusion of the study.

Additionally, we believe that the FDA should clarify that:

1. Interchangeability does not represent a higher standard of safety or clinical effectiveness - all biologics approved by FDA are safe, pure and potent for their intended use. Consequently interchangeability is a requirement for additional data, not a different standard, and that
2. Interchangeable biologics and biosimilars must be manufactured to the same quality levels as are applied to originator biologics.[53]

Lastly, a Part 15 Hearing is not needed to obtain public input on the concept of interchangeability. As a matter of regulatory process, public input will be provided in a comprehensive manner by providing written comments on a Draft FDA guidance on this topic.

We encourage the careful but ongoing process by which the Agency is implementing the regulatory framework to allow safe and effective biosimilars to become available for US patients. We believe that the Agency's approach for the biosimilar development process for biosimilars and interchangeable biologics provides reassurance to prescribers, patients and other stakeholders as to the quality of these products, with ongoing draft guidances scheduled for release in 2016.[54].

We want to thank FDA for the time and interest the Agency is taking in reviewing our biosimilar applications and we look forward to working with the Agency in the future on many more biosimilar development programs so that Americans can enjoy the benefits of the biosimilar and interchangeable biologics pathway offered in BPCIA. This will enable patients in the U.S. to achieve greater access to these often life-saving biological medicines, knowing that they will be of

[53] FDA Guidance for Industry, "Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product", April 2015. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291134.pdf (Accessed March 18, 2016);

[54] Guidance Agenda: New & Revised Draft Guidances CDER is Planning to Publish During Calendar Year 2016. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm417290.pdf (Accessed March 18, 2016).

the same quality, and as safe, pure and potent as their reference products. Consistency in the development, regulatory review and approval of biosimilars and interchangeable biologics can instill confidence regarding biosimilars in U.S. patients and physicians just as has occurred in Europe and elsewhere. Only then will the public health benefit offered by biosimilars be more broadly and fully realized. With the unique authority to designate interchangeable biologics granted to FDA by Congress in BPCIA, we have every confidence that the Agency can further show how scientific progress can be used to assure consistently high quality biosimilars and interchangeable biologics are available to US patients.

Yours sincerely,

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Acronyms:

ACR	American Colleague of Rheumatology
AE	Adverse event
BPCIA	Biologics Price, Competition and Innovation Act
CP	Citizens Petition
ECCO	European Crohn's and Colitis Organisation
EMA	European Medicines Agency
EU	European Union
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
PD	Pharmacodynamics
PK	Pharmacokinetics
TNF	Tumor Necrosis Factor