10 May 2017

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

RE: FDA Draft Guidance for Industry Considerations in Demonstrating Interchangeability With a Reference Product; Docket number: FDA-2017-D-0154

Dear Sir/Madam,

Sandoz, a Novartis division, submits the enclosed comments in response to Food and Drug Administration’s (“FDA’s”) Draft Guidance entitled “Considerations in Demonstrating Interchangeability With a Reference Product” (“Draft Guidance”)¹ Docket No. FDA-2017-D-0154, published on January 17, 2017.²

We welcome the issuance of Draft Guidance that provides the Agency’s current thinking and some regulatory expectations for the development of interchangeable biologics. We appreciate the opportunity to comment and have a number of recommendations that we offer for the Agency’s consideration as it finalizes its guidance on this important topic.

Our comment letter is divided into three sections:
1. General comments on important topics raised by the Draft Guidance
2. A table containing recommendations to amend specific lines of the Draft Guidance

Sandoz has extensively discussed the topic of interchangeability in a submission of March 22, 2016 (FDA-2015-P-4935-003³) in which we commented on a Citizen Petition submitted to the Agency by AbbVie⁴. We reference our March 22, 2016 submission as an integral portion of this comment letter, along with all cross-references contained therein.

1. General comments:

A. Interchangeability is a requirement for additional data not a higher standard

We believe it is critical that the Agency clarify that interchangeability is a requirement for additional data and does not represent a higher standard for the product itself. It is important for stakeholders across the health care industry to understand that FDA does not have more than one standard of product quality for

the approval of biologics and that the safety and efficacy profiles of a biosimilar is the same once it is designated as an interchangeable biologic.

Any suggestion that a biosimilar is somehow less safe and effective before it is designated as an interchangeable biologic is clearly an inappropriate conclusion since it is the very same product (molecule and formulation). Further, interchangeable biologics and biosimilars must be manufactured to the same quality standards as all biological products licensed by FDA. 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 inspected and licensed based on FDA’s regulatory requirements, and the standards for manufacturing establishments that produce biosimilars and interchangeable biologics are identical as those applied to facilities used in the manufacture of reference products.

For instance, while the Draft Guidance clearly calls for clinical studies with very specific endpoints (pharmacokinetics (PK) and if appropriate, pharmacodynamics (PD)) and potentially for comparative human factor studies of the administration device, it also discusses extensively the analytical quality requirements, including “finger-print like similarity.” We appreciate that the FDA is using this term to refer to extremely close concordance of reference product and the potential interchangeable biologic. But the Final Guidance must be clear that discussion of fingerprint-like similarity does not imply that there is a higher standard for interchangeable biologics as compared to biosimilars, nor that a biosimilar that is not designated as “fingerprint-like” but that is approved by the Agency is somehow “less similar or good” when administered to patients and cannot subsequently be designated as interchangeable. One way to ensure greater clarity about this topic and avoid misconceptions is to define “fingerprint-like similarity” with respect to FDA’s review of interchangeable biologics.

In sum, all approved biosimilars have achieved the same standard of safety and efficacy as their reference product. Further, it is important for the Agency to be clear that there are not distinct product quality standards for reference products, biosimilars and interchangeable biologics, as all biologics are licensed based on the same rigorous regulatory standards of the FDA. The standard applied by FDA is consistent, and this is critical to the confidence of patients and their providers in the ultimate product approved, and integral to the confidence held by all for the FDA approval decision itself.

When considering interchangeable biologics and biosimilars, it is important to be clear that interchangeable biologics are not products of higher quality, and it is clear from the statutory language that this was never the intent. Rather, much like an A-rating in the Orange Book, an interchangeability designation in the Purple Book represents additional information available to pharmacists. Perpetuation of these misunderstandings could negatively impact access to these important biologics medicines. Accordingly, we suggest that the FDA add an explanation in the Introduction of the Final Guidance that

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5 21 CFR 601.20 Biologics licenses: Issuance and conditions
6 Given that FDA has yet to make a determination on the non-proprietary naming conventions for interchangeable biologics we incorporate by reference the previous Novartis/Sandoz comments, and all references therein, to the FDA dockets on the nonproprietary naming of biological products (FDA-2013-D-1543; FDA-2015-N-0648) as well as those matters raised in the citizen petitions on the same topic (FDA-2013-P-1398; FDA-2013-P-1153).
8 FDA Guidance for Industry: Quality considerations in demonstrating biosimilarity of a therapeutic protein to a reference standard (April 2015)
12 Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). Available at: https://www.fda.gov/drugs/informationondrugs/ucm129662.htm (accessed February 17, 2017)
clearly states that an interchangeability designation requires additional data but does not represent a higher standard for product quality or safety and efficacy beyond that required to meet a biosimilarity designation.

B. Extrapolation is based on molecular “sameness” and applies to interchangeable biologics in the same manner as it does to biosimilars

We strongly endorse the Agency’s position articulated in the Draft Guidance that the concept of extrapolation is applicable to interchangeable biologics. Extrapolation is based on (1) the totality of data obtained comparing the biosimilar or interchangeable biologic to the reference product as well as (2) a scientific justification for each indication for which extrapolation is sought. There is no scientific reason why the concept of extrapolation should be different in the setting of interchangeability as compared to biosimilarity.

We recognize that it is anticipated that most sponsors will use the 2-step approach of pursuing an approval of a biosimilar first, while seeking appropriate indications of the reference product where scientifically justified, and then applying for an interchangeable designation. An interchangeable biologic will be expected to be designated as interchangeable for all the indications for which it is already approved and labelled as biosimilar.

C. Immunogenicity is at present a hypothetical concern that is not supported by existing data

The general position of the Agency, as outlined in the Draft Guidance is that there may be “subtle differences”\(^\text{14}\) between a reference product and an interchangeable biologic that upon repeated switching may elicit a new and unique immune response. It is important to note that immunogenicity concerns with biosimilars, including switching of biosimilars, are hypothetical only, and to date there is no existing data documenting these concerns. This includes extensive use of marketed biosimilars for the past decade in the EU.

An elevated immune response caused by exposure to a biosimilar is highly unlikely as comparable immunogenicity has to be demonstrated by data which includes pre-approval clinical studies prior to biosimilar approval.

To put immunogenicity of biological drugs into perspective based on decades of regulatory and clinical experience with these products, the greatest risk of immunogenicity is related to the protein backbone of the product – namely, its primary, secondary and tertiary structure. This risk is first encountered when the reference product is commercially launched and becomes widely used. By the time that a biosimilar or interchangeable biologic is developed to the reference product, sponsors and regulatory authorities already have a clear picture of the immunogenicity related to the protein structure. However, since biosimilars or interchangeable biologics must have identical amino acid sequences as their reference biologic and a higher order structure that is indistinguishable from that of their reference biologic, any residual risk of immunogenicity of a biosimilar or interchangeable biologic can only be due to different post-translational modifications or a different impurity profile. While not negating this risk, it is certainly lower than the immunogenicity risk of a new originator biologic when it is first launched, prior to availability of post-approval pharmacovigilance data.

The need to carefully monitor safety applies to all biologics, and not just biosimilars or interchangeable biologics. All biologics must be manufactured under current good manufacturing practices (cGMP)\(^\text{15}\) and


\(^{15}\) 21 Code of Federal Regulation’s § 211 - Current good manufacturing practice in manufacturing, processing, packing, or holding of drugs and 21 Code of Federal Regulation’s § 211 Current good manufacturing practice for finished pharmaceuticals
these quality requirements should not be confused with the highly similar analytical standard fundamental to the initial approval of biosimilars and interchangeable biologics.

It is well known that some immunogenic responses to a biologic may first occur only after extended exposure of months, which has led to recommendations in some cases for monitoring up to one year after initial dosing.\(^\text{16}\) This observation after extended use of a biologic is independent of a switching event (either between batches of the same product, pre- and post-manufacturing change, or product developed by different manufacturers as either a related standalone biologic or as a biosimilar). In addition, it is likely that antibodies elicited by a reference product will also be cross-reactive to a corresponding biosimilar or interchangeable biologic and vice versa. This is to be expected given the identical amino acid structure and the indistinguishable three-dimensional conformation of a biosimilar as compared to its reference product. Two recent studies have in fact demonstrated that this is the case with infliximab manufactured by the originator and by a biosimilar manufacturer, providing evidence that biosimilar and reference biologic are highly similar in their ability to elicit an immune response.\(^\text{17}\) Considering the fact that immunogenicity can develop over time and that the immune response to a reference biologic and its biosimilar are highly similar, it would be a mistake to ascribe appearance of immunogenicity after multiple switches solely to the switching of products. But it must be acknowledged that this is a hypothetical concern only that has not been detected to date in any clinical trial or real-world setting.

Sandoz’s own extensive post-marketing experience in Europe with biosimilars (including a glycoprotein) including over 340 million patient days of exposure with Sandoz biosimilars has not revealed any unexpected safety concerns of any nature including immunogenicity or a loss of efficacy.\(^\text{18}\) Additional high quality data are available with other products, including the NOR-SWITCH randomized clinical trial\(^\text{19}\) and the DAN-BIO registry study.\(^\text{20}\) We understand that the practice of medicine in many European countries has included multiple switching events for multiple products, including biologics that are known after many years of use (after initial licensure) to be inherently immunogenic as well as biologics that have low inherent immunogenicity. The European experience with biosimilars represents a safety data set that is supportive of the safe use of biosimilars including switching and interchangeability events.\(^\text{21}\) A recent review by respected European health authority experts concluded as a scientific and clinical matter that “Our conclusion is that biosimilars licensed in the EU are interchangeable.”\(^\text{22, 23}\)

It is a fact that situations analogous to the multiple switching of interchangeable biologics have already occurred without incident with respect to immunogenicity. Manufacturing changes are normal and common as a part of the life cycle of a given biologic. Manufacturing changes may be made for a wide variety of reasons,\(^\text{24}\) including but not limited to modernization of equipment and analytical methodology, replacement of sources of raw materials or perhaps in the nature of the raw materials, upgrading of facilities and introduction of wholly new facilities. At times the changes may be more substantial, such as

\(^\text{17}\) MB Ruiz-Arguello, et al., \textit{Antibodies to infliximab in Remicade\textsuperscript{a}-treated rheumatic patients show identical reactivity towards biosimilars, Ann Rheum Dis} (2016) 75(9) 1693-1696 and S Ben-Horin, et al., \textit{Cross-immunogenicity: antibodies to infliximab in Remicade\textsuperscript{a}-treated patients with IBD similarly recognise the biosimilar Remsima\textsuperscript{a}} \textit{Gut} (2016) 65:1132-1138
\(^\text{18}\) Sandoz data on file, as submitted to the European Medicines Agency as Periodic Safety Update Reports for Binocrit\textsuperscript{a}, Omnitrop\textsuperscript{a} and Zarzio\textsuperscript{a}, up to 4Q2016.
\(^\text{19}\) B Glintborg et al. \textit{Abstract OP0225, presented EULAR Congress 2016}
\(^\text{21}\) In the European Union, ‘interchangeability’ means the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of, the prescriber. The decision by the treating physician to exchange one medicine with another medicine with the same therapeutic intent in a given patient is referred to as ‘switching.’ European Commission, DG Enterprise and industry. \textit{What you Need to Know about Biosimilar Medicinal Products. Process on Corporate Responsibility in the Field of Pharmaceuticals Access to Medicines in Europe. A Consensus Information Document, 2013.}
\(^\text{23}\) The European Medicines Agency has no legal authority to grant an interchangeability designation because interchangeability is the responsibility of individual member countries.
but not limited to introduction of new cell banks or introduction or replacement of new manufacturing steps. But all changes have the potential to introduce structural changes or changes in process residuals, and the manufacturer must always provide evidence to the Agency that safety and efficacy are not impacted as compared to the safety and efficacy profile first established at the time of initial approval. We have analysed batches of originator biologics over time and have detected structural and functional changes that correlate with publicly revealed manufacturing changes in the EU, and that are shown in products also sourced for the US. Given the multi-year shelf life of most marketed biologics, there is no doubt that batches of biologics manufactured prior to and after implementation of process changes are both on the market at the same time. It is almost certain that patients have switched back and forth between such batches. To the best of our knowledge, there have been no reports of immunogenicity despite the clear evidence that quality attributes of the biologic have changed over time. This is relevant, real world evidence that the hypothetical increase in immunogenicity has not been detected with dozens of different US licensed biologics for which variants may have been used “interchangeably,” despite the product quality changes (including “subtle changes”) that the Agency suggests may be of concern.

We recognize that biosimilars and interchangeable biologics are new concepts in the US and as such are being subjected to a very high level of precaution. But hypothetical immunogenicity concerns may have already led many potential patient and physicians to be fearful of biosimilars, and this in turn will slow acceptance of these products. It is important the Agency clarify in the Final Guidance and in other public education materials that immunogenicity concerns are still only hypothetical and have not been substantiated by any evidence. Clarification of these points is critical to acceptance of biosimilars and interchangeable biologics, a goal that the Agency shares with patients, Congress and the U.S. healthcare community.

D. Requirement for study with PK/PD endpoints to demonstrate interchangeability

The FDA draft guidance recommends the use of PK or if relevant, a PD endpoint(s) as primary endpoints for demonstration of interchangeability:

“The primary endpoint in a switching study or studies should assess the impact of switching or alternating between use of the proposed interchangeable product and the reference product on clinical pharmacokinetics and pharmacodynamics (if available), because these assessments are generally most likely to be sensitive to changes in immunogenicity and/or exposure that may arise as a result of alternating or switching.”

In addition, the Agency requests that such studies be conducted in patients instead of healthy subjects:

“FDA strongly recommends that sponsors use patients in switching studies because these studies are designed to mimic how the proposed interchangeable product will be used in clinical practice.”

From a scientific perspective, the most sensitive methods to detect antibodies are immunoassays that are designed explicitly to detect antibody molecules. There are many potential formats for such assays, and such assays can be validated. It is also generally accepted that healthy subjects are most likely to show the greatest immunological responses. Both aspects have already been articulated by the Agency in the Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products (August 2014):

“In terms of evaluating the clinical relevance of immune responses, the Agency has the following recommendations:

Development of assays for anti-drug antibody (ADA)

Sponsors should develop and implement sensitive immunoassays commensurate with the overall product development program. Concomitant assessment of levels of therapeutic protein product in the sample is recommended to assess the potential for the presence of the product to interfere with detection of antibody in the assay.”

“Patients who are immune suppressed may be at lower risk of mounting immune responses to therapeutic protein products compared to healthy volunteers with intact immune responses”

We understand that the sensitivity the Agency is referring to is not detection of antibodies per se, but is instead the ability to detect a clinically significant event that may be caused by changes in immunogenicity.

However, immunogenic events with significant safety sequelae may occur without impacting PK or PD. As noted in Section 1C above, these include (but not be limited to) neutralizing antibodies that interact with endogenous proteins and neutralizing antibodies that bind to the active site of the biologic (thereby impacting efficacy) but that do not impact the clearance rate of the biologic. PK or PD studies would not detect these types of immunogenicity.

In addition, it is also possible that changes may be detected in PK or PD that are not linked in any manner to immunogenicity but to changes in the underlying disease or concomitant medication. One such example is the fact that in individual patients with active disease, the PK response to given antigen may vary with time, with drug clearance rates either increasing or decreasing. It would be misguided to assume that changes in PK or PD rates in patients who are suffering from active disease correlates with changes in immunogenicity as the PK or PD changes in these patients may be reflective of changes in underlying physiology. One way to avoid this confounding factor might be to conduct the switching studies in healthy subjects. This is in fact the recommendation from the Agency in the Final Guidance entitled “Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product” (December 2016) that states:

“A study in healthy subjects is considered to be more sensitive in evaluating the product similarity because it is likely to produce less PK and/or PD variability compared with a study in patients with potential confounding factors such as underlying and/or concomitant disease and concomitant medications.”

Given the reasons provided above, the impact of changes in immunogenicity on PK described in the scientific literature for immunogenic biologics is not sufficiently strong to justify the use of PK parameters in all cases as primary endpoint(s) applying standard bioequivalence criteria.

Furthermore, the Agency’s current recommendation of using PK and/or PD as primary endpoints in switching studies for a proposed interchangeable product, will not be applicable for all biologic products. Following intravitreal injection, monoclonal antibodies (mAbs) and/or fusion proteins used in ocular indications, cross the -retinal-blood barrier only in low amounts, leading to very low systemic drug levels. Thus, a meaningful assessment of systemic PK and/or PD endpoints cannot be carried out for these types of biologics following this extra-vasal route of administration.

Of note, the recommendation to capture almost entire PK profile (≥3x t₁/₂) with intensive PK sampling may require hospitalization of patients, potentially including overnight stays in order to control for variability in PK endpoints for which the study will be powered for. The repeated, prolonged hospitalization/in-house periods are likely to increase patient burden and may be problematic from the patient’s benefit-risk perspective, in particular in fragile, higher-risk patient populations, such as oncologic and/or profoundly immunosuppressed patients.
The clinical utility of therapeutic drug monitoring (typically C\text{trough}) and ADA assessments has been demonstrated in patients with inflammatory bowel diseases treated with the highly immunogenic anti-TNF-\(\alpha\) mAbs \(^{26}\).

“Sparse” PK sampling (limited sampling, but targeting important parameters) is also used in clinical practice to guide the selection of appropriate dosing and the overall therapeutic strategy.

In the light of all considerations described above, instead of conducting a switching study with PK or PD primary endpoints that contains an assessment of PK bioequivalence necessitating intensive PK sampling, we recommend an alternative design for the switching study that contains three elements:
1. Utilization of an efficacy or validated alternative biomarker
2. with sparse PK sampling (e.g. measure C\text{trough} levels if applicable) following sequential switches,
3. together with immunoassays to detect circulating antibodies (and if present, neutralizing antibodies).

The utilization of immunoassays to assess samples from all study participants is a direct measure of whether or not multiple switches between reference product and the proposed interchangeable biologic triggers an immune response that is not elicited by uninterrupted use of the reference product.

**E. Use of a U.S. licensed reference product in a switching study or studies**

The Draft Guidance strongly suggests that a US-licensed reference product be used in the clinical studies conducted to establish interchangeability. We have concerns with this suggestion and would encourage the FDA to reconsider it in final guidance. The draft guidance focuses on two reasons:
1. There may be subtle differences between the reference product and the biosimilar that may prime the immune system in such a manner so that multiple exposures to both products can elicit an increase in the overall immune response, and
2. There may be multiple versions of a non-US licensed reference product on the international market, with possible subtle differences with the US-licensed reference product and with each other.

**Stated concern #1**

The stated concern that there may be subtle differences that are immunologically relevant hinges on a premise that there are differences between a reference product and its biosimilar that may be present but that are not detected analytically. This premise is antithetical to the foundation of biosimilarity, as well as to the collective regulatory experience with use of comparability to approve manufacturing changes for all biologics. The essential foundation of the biosimilar concept is that analytical methodologies provide complete ability to detect subtle differences when comparing reference product and biosimilar, and that these are sufficient to provide the foundation of biosimilarity\(^{27}\). Notably, this same concept applies to each reference product or any given biosimilar, individually and over time, and is core to the concept of comparability used in support of manufacturing changes over the life time of any given biologic\(^{28, 29, 30}\).

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Experience in the 20 years since FDA issued the Comparability Protocol in 1996\(^{31}\), subsequently adopted as ICH Q5E, support that conclusion. Importantly, the reference products for many biosimilars have undergone multiple manufacturing changes in series (up to 50 in one instance for one biologic approved and marketed in US, EU and many other countries, and that is being used as a reference product for development of biosimilars)\(^{32}\) and no meaningful clinical differences have been identified. These manufacturing changes are based on the same highly similar analytical standards codified in BPCIA\(^{33}\), and in those instances it is rare for any clinical trials to be required at all\(^{34}\). It is accepted that pre- and post-manufacturing changes to a biologic are fully interchangeable with themselves and always maintain all indications (“complete extrapolation”) once the agency approves. The label on these products does not change.

The suggestion that there are relevant differences that are not detected by analytical techniques implies that there may be a potential difference in quality attributes between a biosimilar and an interchangeable biologic (even though an interchangeable biologic is structurally and functionally identical to the biosimilar, being simply the biosimilar on which additional switching studies have been conducted – the product itself has not changed \(^{35}\)). As described in Section 1A above, we believe that a designation of interchangeability is a regulatory requirement for additional clinical data related to multiple switches of reference product and biosimilar, as mandated in BPCIA, which will then enable a Purple Book listing that pharmacists (subject to state law) can reference.

**Stated concern #2:**

The draft guidance indicates that “there may be multiple versions of a non-US licensed reference product on the international market, with possible subtle differences with the US-licensed reference product and with each other.” As a result, sponsors are strongly urged to use a US-licensed reference product, although the Draft Guidance provides the possibility that a non-US-licensed reference product may be used if a sponsor provides the Agency with “adequate scientific justification.”\(^{36}\)

Almost all biologics marketed in the U.S. are also licensed and marketed outside of the U.S. We are unaware of any data suggesting that there are any product quality differences that may lead to a difference in immunogenicity (either in absolute rate or the quality of the immune response) between a US-sourced and ex-US sourced product. Indeed they are often made at the same facility and often in highly regulated countries that apply high cGMP standards.

The guidance’s recommendation to use U.S. sourced reference product will have a serious impact on the feasibility of conducting the study recommended by in the Draft Guidance. In our development programs, we have become keenly aware of the difficulty and much greater expense of purchasing large quantities of reference product in the US. There are a multitude of steps that can be taken by reference product sponsors to limit supply of those products, and such steps have already been taken aggressively. It is not possible to minimize the impact of lack of timely supply of reference product material on the ability of any sponsor to undertake clinical studies, especially those involving multiple switches over long periods of time. Given that patients must be continually treated, if reference product is not available when needed, those patients must be dropped from the study.

While it is true that multiple versions of a reference product may be available in different markets (although it is more likely to be a difference in specifications as opposed to a difference in quality), there

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are measures that a sponsor can take to minimize and perhaps avoid these circumstances, such as consistently obtaining reference product material from the same country or region for the studies supporting both biosimilarity and interchangeability. In particular, if the sponsor conducted extensive analytical bridging to justify use of a specific ex-US reference product to support initial approval of a biologic as a biosimilar, then it is reasonable to accept use of reference product material sourced from the same market in studies to establish interchangeability.

In sum:
1. We strongly suggest that the Final Guidance provide greater openness and flexibility to accept use of non-US licensed reference product to seek approval of an interchangeable biologic in the US if scientifically justified.
2. We recommend that in the Final Guidance the Agency should provide specific criteria for scientifically justifying the use of ex-US reference product.
3. We also recommend that in the studies conducted to establish interchangeability, that sponsors be permitted to use reference product sourced from the same market as was used in studies establishing biosimilarity.

F. Comparative use human factors studies with statistical analysis

We support the Agency’s recommendation to use a threshold analysis to understand if the presentation of the interchangeable biologics has minor, moderate or major difference from the originator’s presentation. However, the specific recommendation to use human factors study with a clinical non-inferiority statistical analysis in the guidance is a new concept and standard that has not previously been applied to pharmaceutical agents. This recommendation is not consistent with the agency’s previous human factor study guidance.

Sandoz believes that a human factor validation study, as already described by the Agency in the guidance ‘Applying Human Factors and Usability Engineering to Medical Devices’, 2016, 37 would provide the greatest value in assessing any potential increased use-related risks associated with the use of the proposed interchangeable product. Elements from this draft guidance include:

- multiple user groups,
- participants experienced with use of the reference biologic or proposed interchangeable product as well as those naive to the use of the reference product,
- with a focus on observing use errors and difficulties, and
- understanding the root cause of those use errors and difficulties.

Consistent with the Final Guidance “Applying Human Factors and Usability Engineering to Medical Devices”, these analyses should be descriptive, and the most important assessment should be whether the presentation of the interchangeable biologics has any negative impact on the use-related risks and not on whether or not the responses are “highly similar”. It then follows that the Final Guidance on Interchangeability should not require the demonstration of non-inferiority in terms of percentage use error with a statistical standard.

This approach would then be consistent with other FDA guidances and FDA recognized standards related to the application of HFE. Sandoz also believes that the agency should encourage the biosimilar sponsor to develop presentations/devices with improved user-device interface wherever possible, but not simply hold to “comparative” or “as similar as possible”.

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37 FDA Guidance for Industry and FDA Staff: Applying Human Factors and Usability Engineering to Medical Devices (Feb 2016).
G. Comparison of Requirements for Interchangeability and for Manufacturing Changes

The Agency recommendations for studies to establish interchangeability are rigorous, including human PK/PD studies, use of US-sourced reference product, collection of immunogenicity data from human studies and human-use factor studies. It should be pointed out that these are being used to evaluate a product that is designed to match the reference biologic as closely as possible.

All of these requirements significantly exceed the Agency’s requirements for evaluation of post-approval manufacturing changes that often lead to changes in critical quality attributes. By definition, drugs (including biological drugs) manufactured after a process change are considered to be interchangeable with material made prior to the process change. The Agency does not notify healthcare professionals or the public of these changes, and no concerns have been raised with regards to this practice.

Post-approval manufacturing changes are common in the life-cycle of biologics. Manufacturing changes may be made for a wide variety of reasons, including but not limited to modernization of equipment and analytical methodology, replacement of sources of raw materials or perhaps in the nature of the raw materials, upgrading of facilities and introduction of new facilities. At times the changes may be more substantial, such as but not limited to introduction of new cell banks or introduction or replacement of new manufacturing steps. While at times clinical trials may be required, the overwhelming majority of manufacturing changes are approved on the basis of comparative analytical data. Further, the Agency has been applying this approach for over two decades without any safety or quality concerns.

While we acknowledge that the BPCIA established a separate category of “interchangeability” in addition to “biosimilarity,” as a matter of scientific principle, we believe that in principle biosimilars seeking an interchangeability designation should not be subjected to rigorous requirements that go beyond those required for process changes for reference products. Given that the draft guidance establishes criteria to differentiate between biosimilarity and interchangeability determinations, we encourage the Agency to consider the recommendations made in this comment letter as they are more consistent with the approach that has been followed for the evaluation and approval of manufacturing changes for reference products.
2. Comments and recommendations for specific lines of the Draft Guidance

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<th>Line Number</th>
<th>Comment and Rationale</th>
<th>Proposed change (if applicable)</th>
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<td>76-83</td>
<td>As noted in the General Comments section of this comment letter, we believe it is important for FDA to clearly articulate that the interchangeability designation is based on additional clinical data, not a requirement for higher standard.</td>
<td>We recommend the final guidance include the following new underlined text in the final guidance: &quot;FDA expects that sponsors will submit data and information to support a showing that the proposed interchangeable product can be expected to produce the same clinical result as the reference product in all of the reference product’s licensed conditions of use. The designation of interchangeability is a requirement that additional data be provided to support the legal requirements for interchangeability as described in the BPCIA, but is not a higher quality, safety and efficacy standard beyond that required to meet a biosimilarity designation.”</td>
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<td>358-362</td>
<td>&quot;The primary endpoint in a switching study or studies should assess the impact of switching or alternating between use of the proposed interchangeable product and the reference product on “clinical pharmacokinetics and pharmacodynamics (if available), because these assessments are “generally most likely to be sensitive to changes in immunogenicity and/or exposure that may arise as a result of alternating or switching.” As written, the Draft Guidance is concerned with “immunogenicity and/or exposure that may arise as a result of alternating or switching&quot;. We believe that changes in immunogenicity that may arise as a result of switching are associated with changes in clinical pharmacokinetics and pharmacodynamics, however the associations between ADA/ADA titers and their impact on PK exposure observed for a number of immunogenic biologic drugs described in the scientific literature is not</td>
<td>Instead of focusing on PK as a surrogate of immunogenicity, we believe the Final Guidance should focus on the totality-of-the-evidence evaluating all aspects that can be impacted by changes in immunogenicity, i.e. efficacy and safety and perhaps supplemented by PK.</td>
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| 382-388 | Dedicated Switching Study Design  
A study with a lead-in period of treatment with the reference product, followed by a randomized two-arm period—with one arm incorporating switching between the proposed interchangeable product and the reference product (switching arm) and the other remaining as a non-switching arm receiving only the reference product (non-switching arm)—may be appropriate when designing a switching study.  
However we believe the lead-in period should not be made mandatory as it is generally known that ADAs can be detected as early as 2 weeks after the first dose. The sponsor should be given an option to justify why a lead-in period may not be necessary. For example, the applicable scenarios are biologics with long half-lives, biologics with long dosing intervals and biologics that do not accumulate during dosing intervals. | We recommend the final guidance include the following new underlined text in the final guidance:  
A study with a lead-in period of treatment with the reference product, followed by a randomized two-arm period—with one arm incorporating switching between the proposed interchangeable product and the reference product (switching arm) and the other remaining as a non-switching arm receiving only the reference product (non-switching arm)—may be appropriate when designing a switching study. A sponsor should provide rationale in the event that they propose not to have a lead-in period for the study. |
| 391-403 | “Sample size: The sample size of the switching study should generally be based on PK considerations (inter-subject variability in AUC_{tau} or C_{max} should be primary considerations) and should be appropriately justified.”  
The sample size recommended by the Draft Guidance for a powered PK study for interchangeability will almost certainly be much larger than required for any trials conducted to establish biosimilarity. As written, it may not be feasible to predict the inter-subject variability in AUC_{tau} and C_{max} in the suggested study setting based on our experience. In addition, literature data describing inter-individual variability of the primary endpoints AUC_{tau} and C_{max} following the proposed study design derived from rich PK sampling is very limited. Therefore, Sandoz is not in a position to provide a robust estimation of the inter-subject variability and in consequence a reliable sample size assessment for the proposed interchangeability study design. | We believe this section of the draft guidance should undergo substantive revisions that incorporate our suggested approach for the assessment of interchangeability that is based on the descriptive evaluation of the totality-of-the-evidence gained from a long-term study in patients comprising:  
- Safety/immunogenicity  
- Efficacy  
We consider the assessment of interchangeability solely based on PK as a surrogate for immunogenicity as not appropriate for establishment of interchangeability.  
Instead, we recommend a safety and efficacy study with immunogenicity assays and with sparse PK sampling. |

Sandoz expects the inter-subject variability for therapeutic proteins, especially for those eliciting an immunological response in patients to be higher as compared to healthy volunteers which form the basis for the assessment of biosimilarity. This is described in FDA’s Guidance on Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (Dec 2016),\(^{39}\) a study in healthy subjects is considered to be more sensitive in evaluating the product similarity because it is likely to produce less PK and/or PD variability compared with a study in patients with potential confounding factors such as active underlying and/or concomitant disease(s) and concomitant medications”.

A study conducted to establish bioequivalence of therapeutic proteins in patients following administration of multiple doses (with intensive PK sampling) after a prolonged treatment duration in order to accommodate a minimum of three switches and of minimum of the half-lives in the last switch, is an entirely new study concept, having no precedence in global drug regulation. Therefore, there is no experience with regards to factors influencing the proposed primary endpoint such as inter-subject variability, changes in body weight over the course of the study, missing data/ drop-out rate etc.

| 449-461 | “If a sponsor is considering a study design using a single study intended to (1) support a demonstration of no clinically meaningful differences between the reference product and the proposed product for biosimilarity and (2) evaluate the impact of switching or alternating between the reference product and the proposed product for interchangeability, an integrated, two-part study design may be appropriate.”

We consider the recommendation to use an integrated two-part study design to support a demonstration of no clinically meaningful differences and to evaluate the impact of switching or alternating between the reference product and the proposed biosimilar product to be problematic (see diagram from Draft Guidance): |

Please note the recommendations included above regarding Lines 391 – 403.

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The guidance states “the subjects in the reference product arm should be re-randomized in the second part of the study to continue to receive the reference product (non-switching reference product arm) or to switch to the proposed product (switching arm).” This means that in the switching part of the study, the initial sample size of the reference product group in part 1 of the study is split into two groups for the second part of the study due to the re-randomization.

For the reasons described in our comments above (391 -403), Sandoz expects that the inter-subject variability of primary PK endpoints following multiple doses in the interchangeability part of an integrated study is higher than following administration of the initial dose in first part of the study conducted to establish biosimilarity. To ensure the sample size is appropriate for both parts of the study (especially in indications requiring prolonged therapy), the powered PK comparison for interchangeability will therefore trigger the sample size of the entire study. Consequently, the equivalence testing for biosimilarity in the first part of the study may be overpowered (due to factoring in dropout rates, study discontinuations, missing data etc.) and the confidence interval will be narrowed. This allows more flexibility of the confidence interval to be placed within the margin range than with a proper sample size for the biosimilar exercise only. Consequently, the reference product and the proposed biosimilar product can differ statistically (90% CI intervals do not include 1.0).

We believe the Draft Guidance gives the impression of a higher standard required for interchangeability than for a demonstration of biosimilarity if the interchangeability aspect drives the sample size for the entire integrated study.
| 427-431 | “..PK, PD, and immunogenicity sampling: To capture the full PK profile, intensive PK sampling should be performed during the last switch interval”  
We believe the recommendation to capture full PK profiles using intensive PK sampling to meet the proposed endpoints may require admission of patients for an in-clinic/house stay (potentially including overnight or longer stay) at least during the initial portion of the blood sampling period post dose. This may prove to be problematic from the patient benefit-risk perspective, in particular in frail, higher-risk patient populations, such as oncologic and/or immunosuppressed patients, where any unnecessary hospitalization may be problematic.  
Many sites participating in a large, integrated two-part Phase 3 study - especially studies in an outpatient setting - would not have the necessary infrastructure (e.g. appropriate facility including specialized equipment; staffing allowing in-house stay of the participating patient(s). Moreover, intensive PK sampling and demanding sample handling procedures may pose significant logistic challenge and require availability and appropriate training of study staff participating in a large Phase 3 trial (i.e. familiarity with PK/PD characterisation studies in the Phase 1 unit setting etc.). It is expected that only a subset of participating sites will be able to take part in the “PK sub study” and that execution of such a substudy of this nature will require significant logistic effort. | Conducting a safety and efficacy study including immunogenicity assessment, as discussed in Section 1D of this comment letter, would mitigate the concerns we have outlined with regards to lines 427-431.  
We recommend sparse PK sampling (e.g. measure C_{trough} levels if applicable) following sequential switches together with immunoassays to detect circulating antibodies (and if present, neutralizing antibodies), instead of intensive PK sampling and assessment of PK bioequivalence. |
| 463-469 | “... the study need to be adequately powered to evaluate pharmacokinetics and pharmacodynamics (if available), …”  
The “Sample size” as well as the “Study Analysis” only focuses on PK while PD should be analysed as secondary endpoints. An adequately powered PD analysis would require a higher sample size that would contradict the approach provided in the “Sample size” and the “Study Analysis” sections. | The study does not need to be adequately powered for PD which means PD should not be part of the primary endpoint. The phrase “and pharmacodynamics (if available)” should be deleted from the sentence in line 466.  
“... the study need to be adequately powered to evaluate pharmacokinetics and pharmacodynamics (if available), …” |
| 519-558 | “…the sponsor may seek licensure of the proposed product as an interchangeable product for one or more additional conditions of use for which the reference product is licensed. | We support the Agency’s position. The Final Guidance should retain the approach to data extrapolation articulated in the Draft Guidance. |
The sponsor would need to provide sufficient scientific justification for extrapolating data to support a determination of interchangeability for each condition of use for which the reference product is licensed and for which licensure as an interchangeable product is sought.

We believe the Draft Guidance provides the necessary flexibility for sponsors to scientifically justify the use of data extrapolation to support a demonstration of interchangeability.

We support extrapolation based on the totality of evidence generated during the development process, which incorporates data from clinical, comparative analytical and pre-clinical studies including knowledge on the mechanism of action and any other factor that may affect the safety and efficacy in each indication. These principles are currently captured in the Draft Guidance.

As stated in Section 1E of this comment letter, sponsors should have the option of using either a US-licensed reference product, or an ex-US reference product as long as the ex-US material is from the same market used to source materials for the biosimilarity studies (analytical, non-clinical, P/PD and clinical confirmation), and for which an analytical bridge was conducted versus US-sourced material.

We recommend revising this section as follows:

However, in a switching study that is designed to evaluate the impact of switching or alternating to support a determination of interchangeability, the comparator product plays a different role. Rather than being used only as a control, the comparator product is used in a switching study in both the active switching arm and the control non-switching arm. Switching studies are designed to assess whether one product will affect the immune system’s response to the other product, once the switch occurs, and whether this will result in differences in immunogenicity or PK profiles. Thus, using a non-U.S.-licensed comparator product generally would not be appropriate in a switching study for the following reasons:

It is possible that the proposed interchangeable product and the non-U.S.-licensed comparator product have, for example, subtle differences in levels of specific structural features (e.g., acidic variants, deamidations). The immune system reaction in terms of the overall level of antibody produced to each product could be similar, thereby supporting a demonstration of no clinically meaningful differences. Thus, these subtle differences would not preclude a demonstration of biosimilarity. However, with switching, multiple exposures to each product can prime the immune system to
recognize subtle differences in structural features between products, and the overall immune response could be increased under these conditions. This immunologic response is highly dependent on the structural differences between the proposed interchangeable product and the comparator product used in the switching study, in addition to other potential differences between the products (e.g., impurities). Because there may be subtle differences between the U.S.-licensed reference product and the non-U.S.-licensed comparator product, there is uncertainty as to whether the results observed in a switching study using a non-U.S.-licensed comparator product would also be observed if the U.S.-licensed reference product had been used instead.

Under the BPCI Act, an interchangeable product may be substituted for the reference product without the prescribing health care provider’s intervention. There may be multiple versions of a non-U.S.-licensed comparator product on the international market, each approved for use by the relevant national regulatory authority and each with possible subtle differences in levels of structural features from the U.S.-licensed reference product and between each other. The goal of a switching study or studies is to determine a biosimilar product’s interchangeability with a reference product that is licensed for use in U.S. clinical settings, thus establishing interchangeability with a product that patients will not receive in the United States would generally not be appropriate.

For these reasons, FDA strongly recommends that sponsors use a U.S.-licensed reference product in a switching study or studies or use reference product materials from the same market used to source materials for the biosimilarity exercise (analytical, non-clinical, P/PD and clinical confirmation), and for which an analytical bridge was conducted to US-sourced material. Sponsors are encouraged to contact FDA early in the product development process to discuss the design of a switching study, including any proposal to provide adequate scientific justification to support the use of data generated in a switching study using a non-U.S.-licensed comparator reference product to support a demonstration of interchangeability.
<table>
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<tr>
<th>641-642 and 647</th>
<th>“The threshold analyses … are recommended for all proposed interchangeable products to identify any difference …”</th>
<th>„The threshold analyses … are recommended for all proposed presentations to identify any difference …”</th>
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A proposed interchangeable product may consist of more than one presentation. The guidance however recommends to assess the differences on the individual presentation level.

<table>
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<tr>
<th>646</th>
<th>“.. data and information from a comparative human factor study.”</th>
<th>“.. data and information from a comparative use human factor study.”</th>
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Consistent use of the term “comparative use human factor study” should be used throughout the guidance.

<table>
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<tr>
<th>678-682</th>
<th>“Differences in the design of the container closure system or delivery device constituent part between the proposed interchangeable product and the reference product may be acceptable provided that the design differences are analyzed appropriately and data are provided to demonstrate that the changes do not negatively impact the ability of end users,”</th>
<th>We recommend the final guidance include the underlined new text:</th>
</tr>
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</table>

The assessment refers to differences, not changes, between presentations of proposed interchangeable products and reference products.

<table>
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<tr>
<th>693-697 and 828-830 and 916-917</th>
<th>693 “These threshold analyses may be used in the development of the proposed presentation to minimize differences between the proposed interchangeable product and the reference product as well as to identify whether additional data, including data from comparative use human factors studies (as described further in this section), may be needed in certain circumstances.”</th>
<th>We recommend the final guidance include the underlined new text where appropriate:</th>
</tr>
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The improvement of the user interface with regard to use safety and effectiveness shall be prioritized over minimization of design differences in particular in cases where differences in design are related to known use problems associated with the reference product.
the data that might be needed to support a demonstration of interchangeability.”

916 “FDA would generally accept a proposed interchangeable product that had the same rates of error as the reference product, as demonstrated by an adequately designed comparative use human factors study or studies.”

We note that, in some cases, the user interface of a reference product may not be optimized with respect to the minimization of use error, and may have residual use-related risk that is considered not to be outweighed by the clinical benefit of using the device (for example a combination product that was developed before human factors and usability standards were in place). In such cases, minimizing the differences of the proposed interchangeable product compared to the reference product is in direct conflict with FDA Final Guidance ‘Applying Human Factors and Usability Engineering to Medical Devices’, 2016, and FDA Draft Guidance, ‘Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development’, 2016, that state that the user interface should be optimized with regard to use safety and effectiveness and that the benefit of product use outweigh the residual risk of the product.

For example, a 2014 study showed that only 16% of epinephrine users used their device properly, 56% of users missed 3 or more steps. The same study indicated that only 9% of metered dose inhaler users used their device properly, 63% of users missed 3 or more steps. ‘Misuse of medical devices: a persistent problem in self-management of asthma and allergic disease’, Bonds, R, published in ‘Annals of Allergy, Asthma & Immunology’, January 2015.

748-750 FDA recommends a side-by-side, line-by-line comparison (between the reference product and the proposed interchangeable product) of the full prescribing information, instructions for use, and descriptions of the container closure systems and/or delivery device constituent parts.”

We recommend the final guidance include the underlined new text:

“FDA recommends a side-by-side, line-by-line comparison (between the reference product and the proposed interchangeable product) of the user interface related aspects of the full prescribing information,
The Draft Guidance recommends a detailed comparison of the full prescribing information (among others). Taking into account that the prescribing information contains ample information which is not related to the design of the presentation and/or the user interface, we consider it appropriate to focus the side-by-side, line-by-line comparison on the user interface section(s) of the full prescribing information.

instructions for use, and descriptions of the container closure systems and/or delivery device constituent parts."

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<th>Row</th>
<th>Comments</th>
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<tr>
<td>803</td>
<td>&quot;Other design differences: FDA may not view a design difference as minor if...&quot;</td>
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<tr>
<td></td>
<td>The Draft Guidance differentiates between minor differences and differences which are considered non-minor. Alternatively the term &quot;Other design difference&quot; is used to describe non minor differences.</td>
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<td></td>
<td>We recommend to use of the terms “minor and non-minor” difference consistently throughout the guidance to describe and classify design differences</td>
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<td>&quot;Non-minor design differences: FDA may not view a design difference as minor if...&quot;</td>
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<tr>
<td>954 - 956</td>
<td>&quot;FDA recommends that patient and caregiver end users (as applicable) of the reference product be considered for inclusion in the comparative use human factors study.&quot;</td>
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<td></td>
<td>Comparative use HF studies will involve participants using the reference product and the proposed interchangeable product (either in a paired design or a parallel design). Inclusion of end users that have prior experience using the reference product may bias comparative use HF studies such that lower error rates are observed with reference product than with the proposed interchangeable product due to familiarity with the reference product. This would undermine the validity of the statistical basis of the non-inferiority analysis. Inclusion of study participants that are naive to the use of the reference product as well as participants naive to the use of the reference and interchangeable product. The observation of use errors, close calls and difficulties, along with the root cause of such observations, should be assessed into context of the overall risk profile of the proposed interchangeable product.&quot;</td>
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<td></td>
<td>Sandoz recommends to modify the guidance by adding the following text:</td>
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<td>“Evidence that end-users can use an interchangeable product safely and effectively without intervention of a health care provider and/or additional training when substituted with the reference product, shall be supported by data from appropriate qualitative HF studies conducted to evaluate use of the proposed interchangeable product. The HF study should include participants experienced with the use of the reference product, as well as participants naive to the use of the reference and interchangeable product. The observation of use errors, close calls and difficulties, along with the root cause of such observations, should be assessed into context of the overall risk profile of the proposed interchangeable product.&quot;</td>
</tr>
</tbody>
</table>
Sandoz believes that a HF Validation study, as described in ‘Applying Human Factors and Usability Engineering to Medical Devices’, 2016, that includes multiple user groups, participants experienced with use of the reference or proposed interchangeable product as well as those naive to the use of the reference product, with a focus on observing use errors and difficulties, and understanding the root cause of those use errors and difficulties, would provide the greatest value in assessing the potential use-related risks associated with the use of the proposed interchangeable product. We believe that the Final Guidance should therefore not require the demonstration of non-inferiority in terms of percentage use error with a statistical standard. This approach would then be consistent with other FDA guidances and FDA recognized standards related to the application of HFE.

If Comparative use HF studies are conducted with participants who are current users of the reference product, observations of incorrect use of the reference product may have significant implications for the health of the participant. The Final Guidance should define whether participants need be retrained in the correct use of their reference product and if so, by whom.

| 902-906 | “The comparative use human factors studies described in this guidance would generally be simulated-use studies where the participants, who are representative of the patients and caregivers, are asked to simulate the use of the product presentations (container closure systems and/or delivery device constituent parts) without actually administering the product.” |

In order to compare use error rates of the proposed interchangeable product to those of the reference product, it is necessary to determine the use error rates of the reference product. To do so, the applicant would need to acquire the reference product and carry out Comparative Use HF studies with the reference product. This would involve using actual devices containing active drug product (defined as ‘Actual-Use’ studies in FDA Draft Guidance for Industry ‘Human Factors Studies and Related Clinical Study Considerations in

We recommend the final guidance include the following change:

“The comparative use human factors studies described in this guidance would generally be “actual use” studies simulated-use studies where the participants, who are representative of the patients and caregivers, are asked to simulate the use of the actual product presentations (container closure systems and/or delivery device constituent parts) without actually administering the product.”
Combination Product Design and Development (Feb 2016).\(^{40}\) However, this contradicts the Draft Guidance on interchangeability that states:

“The comparative use human factors studies described in this guidance would generally be simulated-use studies where the participants, who are representative of the patients and caregivers, are asked to simulate the use of the product presentations (container closure systems and/or delivery device constituent parts) without actually administering the product.” \(^{41}\)

FDA’s Draft Guidance for industry ‘Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development’ defines HF Actual-Use Validation studies as ‘either (1) use the final finished combination product (including the drug, not a placebo) in a simulated use setting or (2) use the final finished combination product in a real (not simulated) environment of use.’

We therefore recommend in the Final Guidance the use of the term ‘actual use’ where noted to be consistent with FDA Draft Guidance for industry ‘Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development’. Otherwise an explicit definition of the term ‘simulated-use studies’ in the context of the comparative use-study should be provided.

918 – 920

“However, we also recognize that lower error rates for a proposed interchangeable product compared to error rates for the reference product would likely not be considered to negatively impact the interchangeability assessment.”

Lower error rates for the proposed interchangeable product seem like a positive outcome for the patient. “...would likely not ...” implies that FDA would sometimes decide that a lower error rate for the proposed interchangeable product could negatively impact the assessment of the interchangeable product.

965 – 966

965 “In determining the margin d, the variability in ERRP should be considered...”

Since analysing the comparative HF study with a clinical statistical standard is a new concept, we would find it very useful if the Final Guidance includes specific examples in the Appendix of the Final

\(^{40}\) Available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm484345.pdf (accessed March 6, 2017)

A standard way of approaching this goal is to fix an NI margin (referred to as d in this appendix) at some fraction of the difference between the placebo effect and the effect of the proposed product. Showing the effect of the proposed product to be significantly better than the margin demonstrates NI. The Draft Guidance for industry Non-Inferiority Clinical Trials discusses meta-analyses and margin selection in detail. A comparative human factors study with an NI design for the purpose of demonstrating interchangeability under section 351(k) of the PHS Act will typically be less complicated than those described in the guidance…"

When considering the necessary sample size for Comparative Use HF studies, it is intended to demonstrate non-inferiority of the proposed interchangeable product within an allowable margin (d). Based on the Draft Guidance, it is not clear how the margin d should be determined or how the assumed reference product use error rate (ERRP) can be determined given that use error rates for the reference product and market complaints are not publicly available.

Guidance for the determination of the reference product use error rate (ERRP) and how a comparative HF study with NI statistical analysis could be designed with adequate power, with examples of potential results and interpretation.

Paired designs and parallel designs are appropriate approaches to the NI studies discussed in this appendix. A paired design in which each end user uses both presentations and acts as his or her own control.”

In paired design studies an individual participant is supposed to use both presentations. The Draft Guidance is silent on the sequence of use (proposed interchangeable product versus reference product) unlike the FDA Draft Guidance on “Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA” which recommends to randomly assign user to the sequence of use (AB or BA).

Please consider revising the text as follows:

“Paired designs and parallel designs are appropriate approaches to the NI studies discussed in this appendix. A paired design in which each end user uses both presentations and acts as his or her own control.”

“For paired design studies, the participants shall be randomly assigned to the sequence of use, such as RP/IP or IP/RP in order to control for the effects associated with order, such as user learning.”

Paired designs and parallel designs are appropriate approaches to the NI studies discussed in this appendix. A paired design in which each end user uses both presentations and acts as his or her own control.”

In paired design studies an individual participant is supposed to use both presentations. The Draft Guidance is silent on the sequence of use (proposed interchangeable product versus reference product) unlike the FDA Draft Guidance on “Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA” which recommends to randomly assign user to the sequence of use (AB or BA).
3. Questions Raised in the Federal Register Notice

In the Federal Register Notice of January 18, 2017 announcing the availability of the Draft Guidance, the Agency posed two questions:

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?*

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

I. Response to the Agency’s Question 1

After approval by the Agency, biosimilars and interchangeable biologics should be held to the same standards and regulated by the same processes that are applied to all biologics. Sandoz believes that it is not necessary to re-establish either biosimilarity or interchangeability once it is initially established with comprehensive and convincing data package. The sponsor of the product, after the change, should demonstrate to the satisfaction of the Agency that the product has the same safety and efficacy profile as established at the time of initial approval, whether it is the originator, biosimilar or an interchangeable biologics.

The underlying concern of this question is that there may be changes in some quality attributes post-approval introduced by CMC changes where after time, there may be differences between the reference product and biosimilar or interchangeable biologic. Post-approval manufacturing changes are common in the life-cycle of biologics. Manufacturing changes may be made for a wide variety of reasons, including but not limited to modernization of equipment and analytical methodology, replacement of sources of raw materials or perhaps in the nature of the raw materials, upgrading of facilities and introduction of new facilities. At times the changes may be more substantial, such as but not limited to introduction of new cell banks or introduction or replacement of new manufacturing steps.

During our development of biosimilars, we have analyzed many batches of reference product over time. We have published data that clearly reveals shifts in several quality attributes over time. Figure 1 illustrates such data obtained with rituximab.42 Recently, Kim et al have published data revealing that some quality attributes of trastuzumab have also changed over time (Figure 2).43 Although the Agency has not yet released guidance on statistical requirements to establish biosimilarity, it is apparent that many of the changes in quality attributes over time are statistically significant. We make a assumption that these observed changes in quality attributes are due to manufacturing changes and that the sponsors of these products have provided data to health authorities justifying these changes, including convincing data that safety and efficacy have not been impacted.

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Figure 1 Acceptable changes in quality attributes of marketed rituximab
Figure 2. Trends of N-glycan attributes of trastuzumab that are related to biological activities by expiry date. [Dotted line shows the min-max range of expiry date prior to August 2018, 1st drift and 2nd drift periods. Boxplot shows the interquartile range, median and outlier (◊). Statistical significance was assessed with one-way ANOVA (*P ≤ 0.05). A) %Afucose, B) %High-mannose, C) %Afucose + %High-mannose and D) %Galactosylation.]

Vezer et al revealed that for biologics licensed in the EU, there have been as many as 50 such manufacturing changes of different types and of different risk levels for some biologics (Figure 3).44 In

all cases the sponsor must prove to the satisfaction of the health authority that the changes have not impacted safety or efficacy. Most of the time these changes are justified by an analytical comparability exercise that bridges material pre-change and material post-change. On rare occasions, a nonclinical study or clinical trial may be required. For those rare occasions when a clinical study is required, it is conducted in a single, sensitive population with results extrapolated to all other indications. In all situations, irrespective of whether an analytical or clinical bridge is conducted, the sponsor does no need to re-establish safety and efficacy. Instead the bridge is designed to demonstrate that the clinical response is the same for material manufactured pre-change and post-change. Effectively, the analytical or clinical bridges establish that the pivotal efficacy and safety studies that were conducted to support initial approval also support the material made after post-approval changes are made.

Figure 3  Number of post-approval manufacturing changes for some EU-approved biologics, according to risk levels

Irrespective of whether the biologic is an originator, a biosimilar or an interchangeable biologic, post approval changes always bridge back to the safety and efficacy data package used for initial approval (illustrated schematically in Figure 4).

Some are asserting that the quality attributes of reference product and biosimilar, or interchangeable biologic must always be highly similar at all times. As can be seen by the data provided in Figures 1 and 2, it is very possible that a given quality attribute may “diverge” over time for a given biologic. Following this assertion, one would call for cross-over comparisons of material prior to a process change, material after a process change and the reference product every time approval is sought for a manufacturing change. But it is crystal clear that this assertion is fatally flawed. All biologicals must always have the same safety and efficacy profile as established at the time of initial approval (Figure 4). There is no basis of any nature to claim that interchangeable biologics are somehow different.
If the Agency were to require re-establishment of interchangeability on a periodic basis, we are cognizant of the likelihood that manufacturers of reference biologics might purposely introduce quality attribute differences to negate prior findings of interchangeability with an interchangeable biologic produced by a different sponsor.

Figure 4. The original safety and efficacy profile remains the source data when justifying post-approval changes in a quality attribute (red bars in Figure 3 represents post-approval changes to a reference biologic and the green bars represent post-approval changes to a corresponding biosimilar or interchangeable biologic)

In summary, if sponsors provide comprehensive data and the Agency has carefully reviewed and approved the post-approval changes, there should be no expectation that a change in the safety or efficacy profile will occur. Accordingly, it is not necessary to re-establish either biosimilarity or interchangeability once it is initially established with comprehensive and convincing data package.

We emphatically believe that no new regulatory processes need to be established beyond those already in place for review and approval of manufacturing changes for all biologics. Otherwise, sponsors of biosimilars and interchangeable biologics would need to frequently repeat the entire totality-of-proof exercise, with the consequence that patient access to these products may be diminished.

II. Response to Agency’s Question 2

Sponsors often evaluate existing products to assess whether they may be useful for treatments of additional indications.

In the event the sponsor of a reference product obtains a new indication that is not covered by pediatric or orphan exclusivity, Sandoz proposes that sponsors of interchangeable biologics should be permitted to submit a request to the agency to obtain the new indication by applying the concept of extrapolation, as the product has already been demonstrated to be interchangeable to the reference product. As a precedent, we propose using the CBE-0 regulatory pathway.
In the supplement submission, no new data or information should be required other than that supporting extrapolation and a revised label adopting the new indication(s) and associated supporting information from the reference biologic label. Irrespective of the regulatory pathway, it is important that the Agency review on the request and act on it expeditiously.

We greatly appreciate the opportunity to contribute to discussions to help define the regulatory expectations to establishing interchangeability in the US. The introduction of interchangeable biologics will enhance use of these therapeutic options and will enable patients to achieve greater access to these often life-saving biological medicines. We are pleased to be at the forefront of these efforts and look forward to continuing to work with the FDA to provide these products to patients in need.

Yours sincerely,

Mark Levick MD, PhD
Global Head of Biopharmaceutical Development
Sandoz Inc.