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Boehringer Ingelheim Pharmaceuticals, Inc.

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Food and Drug Administration
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To Whom It May Concern:

RE: Docket # FDA-2017-D-0154
Considerations in Demonstrating Interchangeability with a Reference Product

Dear Sir or Madam,

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) is pleased to submit comments on the Food and Drug Administration's ("FDA" or "the Agency") Draft Guidance "Considerations in Demonstrating Interchangeability With a Reference Product,"[1] ("Draft Guidance") as published in the Federal Register on January 18, 2017.[2] BI is pleased that the Agency has released this Draft Guidance and we look forward to working in partnership with the Agency on refining the considerations around Interchangeability.

BI is a leading global research organization with extensive expertise developing therapies to treat a variety of chronic and life-threatening diseases. As a global sponsor of both novel biologics and biosimilar products, we welcome FDA's issuance of this Draft Guidance and support FDA's efforts to assist biosimilar sponsors and other stakeholders by defining what the Agency will likely require to demonstrate interchangeability and obtain an FDA designation of interchangeable biologic in the FDA's Purple Book[3].

[1] FDA Draft Guidance, "Considerations in Demonstrating Interchangeability With a Reference Product", January 2017, available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf . Accessed February 20, 2017.

[2] Considerations in Demonstrating Interchangeability With a Reference Product. Federal Register Website, available at: https://www.gpo.gov/fdsys/pkg/FR-2017-01-18/pdf/2017-01042.pdf. Published January 18, 2017. Accessed February 20, 2017.

[3] Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations., available at https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm (accessed February 22, 2017).

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Although BI appreciates that the Agency believes that obtaining an interchangeability designation is possible, we remain concerned that the complexity of requirements that will satisfy a "totality of the data" proposed for demonstrating interchangeability, and resolve what the FDA designates as "residual uncertainty", are still arbitrarily defined and burdensome. More importantly, an approved biosimilar product will have already met the criteria for biosimilarity, including an assessment by FDA that it is "highly similar" to the reference product, and is not of inferior quality to any biosimilar product that is also interchangeable. It is critical that the designation of interchangeability by FDA not be misinterpreted as designating a superior or higher quality product to an approved biosimilar that is not interchangeable. Patients, health care providers, and payors should have full confidence in the safety and efficacy of FDA approved biosimilar products. All biologics are approved to a single standard, and as such all stakeholders should have the same confidence in the quality of any biologic, biosimilar or interchangeable biologic approved by FDA. BI remains concerned that some readers may view the Draft Guidance as erroneously implying that interchangeable products are of a higher quality than biosimilars not (yet) designed by FDA as interchangeable. It is critical that such an implication is absent from this future Guidance and absent from all FDA messaging regarding interchangeable biologics.

BI recognizes that the Draft Guidance is an opportunity to provide feedback on FDA's current thinking on the development of interchangeable biosimilars. Interchangeability is an important consideration for biosimilar manufacturers as it is the catalyst for automatic substitution at the pharmacy level. As such, it is important that the Agency find an appropriate balance between setting an appropriately high bar for interchangeability and not making it impossible to achieve.

Specific BI Comments to the Draft Guidance:

The FDA acknowledges that the sole purpose of a designation of interchangeability is to support substituted prescribing without the intervention of a health care provider (Line 134-135). To this end, the FDA proposes what BI believes is a complex and burdensome analytical approach to "detect and characterize all relevant structural and functional differences between the reference product and the proposed interchangeable product." (Line 191-193). The Draft Guidance describes the potential attributes of additional analytical evaluations that could resolve "residual uncertainty" without acknowledgment that variability among different batches of the approved reference biologic can be significant. [This is particularly evident over time.] For example, shifts in glycosylation (structure), pattern results in different potency in cell-based assays (function), and changes in manufacturing process, all result in differences between the originally approved reference biologic and the currently manufactured reference biologic, but FDA does not question interchangeability from the originally approved reference product. In fact, differences between the originally approved reference biologic and post-change versions of reference biologics are sometimes greater than the differences between the reference product and biosimilar.

BI encourages the FDA to remain flexible in its approach to interchangeability and to lessen the burden of requirements for complex analytical assessments that may not be clinically relevant for demonstrating interchangeable safety and efficacy of approved biosimilars for use in an individual patient. We support the FDA acknowledgement that "the data and information necessary to support

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a demonstration of interchangeability needs to be considered on a case-by-case basis." (Line 261-262), and that reasonably, "data and information acquired from a switching study or studies will be useful in assessing the risk, in terms of safety and diminished efficacy, of alternating or switching between the products." (Line 128-130).

We applaud the FDA's openness to consider circumstances where post-marketing data may provide support for a designation of interchangeability for an approved biosimilar. Further, we believe that there is potential in integrated health delivery systems databases to provide such real world data (RWD) from the US. Additionally, data from another highly regulated market with established high quality pharmacovigilance systems using the same product under the same circumstances, could contribute to the overall biosimilar or interchangeable biologic data package, and should be considered. Such data, in addition to data from a switching study or studies, should be useful in assessing risk and resolving residual uncertainties.

We also applaud the FDA's openness to consider "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." (Line 526-528).

On the device side of the combination product (CP), quantitative studies are inappropriate as applied to usability studies, which is consistent with FDA's historical position. Aside from the practical difficulties of sourcing and using reference products in a study, the position in usability and interchangeability studies using biosimilar CPs should be that reference product users are recruited as subjects in the summative usability study. The summative study demonstrating safety and efficacy can also demonstrate interchangeability by focusing on the users and their interaction with the biosimilar CP where reference product users and non-reference product users can be compared in terms of use errors, close calls and difficulties in a qualitative way, as is the norm. (Lines 615-865)

BI would implore the Agency to regulate post-approval manufacturing changes of interchangeable products as it does for any biologic. Note: the Federal Register Notice announcing the issuance of the Draft Guidance includes the following question[4]:

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

[4] Considerations in Demonstrating Interchangeability With a Reference Product. Federal Register Website, available at: https://www.gpo.gov/fdsys/pkg/FR-2017-01-18/pdf/2017-01042.pdf. Published January 18, 2017. Accessed February 20, 2017.

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recommendations, as well as recommendations for processes and systems (including key logistics) to implement your recommendations.

We believe that no distinction exists between originator biologics, biosimilars and interchangeable biologics that warrant disparate treatment for interchangeable biologics regarding how FDA regulates post-approval manufacturing changes. Consistent use of the scientific and regulatory principles currently used for all biologics, including comparability assessments, should continue to apply to all biologics, including interchangeable biologics. Given that an FDA-approved biosimilar, by definition, is expected to have no clinically meaningful differences from its reference product[5] and an FDA-designated interchangeable biologic, by definition, can be predicted to have the same results in any given patient[6], there is no scientific or regulatory justification for treating these products any differently than any other biologic.

Consequently, once approved, FDA should regulate the reference product and the biosimilar or interchangeable biologic as separate products. To the extent that comparability is used in support of manufacturing changes, the Agency should evaluate the pre- and post-manufacturing change reference product, biosimilar or interchangeable biologic on critical product quality attributes, which ensures that these products (all biologics) continue to behave clinically as expected. Comparability[7] is an established regulatory concept[8] that is accepted for the reference products. If the reference product updates its' dosing or changes its' formulation but does not do so under a new BLA, the concepts of biosimilarity and comparability should hold true and not require changes to the approved biosimilar product or to changes to maintain its approval as an interchangeable biosimilar. Also, changes in the reference product formulation prior to the launch of an interchangeable biosimilar should not introduce a new regulatory hurdle for biosimilar developers.

In sum, BI does not believe there are any "considerations in addition to comparability assessments that FDA should consider in regulating post-approval manufacturing changes of interchangeable products. We are concerned that any additional requirements above and beyond those for comparability assessments used today would significantly and unnecessarily increase the burden to sponsors of interchangeable biologics. Furthermore, a conclusion that additional requirements are needed for interchangeable biologics could also suggest that the comparability decisions themselves may have been inappropriate, and lead to reduced confidence in the originator product used as reference for the biosimilar.

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[5] See definition of biosimilar. TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition And Innovation (BPCIA) provisions of the Patient Protection and Affordable Care Act (PPACA) Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed February 17, 2017)

[6] See definition of interchangeable biologic. TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition And Innovation (BPCIA) provisions of the Patient Protection and Affordable Care Act (PPACA) Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed February 17, 2017)

[7] ICH Q5E "Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process", 2005 available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf (accessed Feb 21, 2017)

[8] Vezér, B. *et al* (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 September 15th , 2016)

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Our understanding is that once FDA has granted an interchangeability designation, it cannot be rescinded because of changes in the reference product. This is because any change in the reference product that fails the comparability assessment would result in a "new" product from the pre-change product[9]. Conversely, if the change in the reference product passes the comparability assessment, the post-change product is expected to behave clinically the same as the pre-change product.

Therefore, because an FDA-approved biosimilar, by definition, has no clinically meaningful differences from its reference product[10] and an FDA-designated interchangeable biologic, by definition, can be predicted to have the same results in any given patient[11], there is no scientific or regulatory justification for treating these products any differently than traditional products approved as standalone biologics under 351(a) with regards to post-manufacturing changes. This is well within FDA's authority and fully aligned with FDA's mission to promote and protect the public health. Indeed, such consistency in the Agency's application of the same scientific principles to all biologics as a regulatory matter fosters the confidence of all stakeholders in all FDA decisions concerning any biologic.

Along similar lines, BI would also implore the Agency to clearly address the addition of new indications secured by the reference product and their applicability to the biosimilar after a designation of interchangeability has been made by the FDA. The Federal Register Notice announcing the issuance of the Draft Guidance also includes the following question[12]:

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

BI believes that no scientific basis exists for a concern regarding newly added conditions of use for the reference product and we do not see any need for FDA to revisit an interchangeability designation after the reference product adds a new indication. The Draft Guidance appropriately

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[9] See Lumizyme® (alglucosidase alfa) and Myozyme® (alglucosidase alfa) scale-up discussion in "Myozyme zig-zags" BioCentury Volume 16, Number 48,Week of October 27, 2008

[10] See definition of biosimilar. TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition And Innovation (BPCIA) provisions of the Patient Protection and Affordable Care Act (PPACA) Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed February 17, 2017)

[11] See definition of interchangeable biologic. TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition And Innovation (BPCIA) provisions of the Patient Protection and Affordable Care Act (PPACA) Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed February 17, 2017)

[12] Considerations in Demonstrating Interchangeability With a Reference Product. Federal Register Website, available at: https://www.gpo.gov/fdsys/pkg/FR-2017-01-18/pdf/2017-01042.pdf. Published January 18, 2017. Accessed February 20, 2017.

allows that FDA may designate a biosimilar as interchangeable even when FDA cannot approve the biosimilar for all of the indications of its reference product (e.g., when unexpired orphan exclusivity protects one or more indications).[13] As noted in the Guidance, an Extrapolation approach to new indications should be possible if supported with scientific justification. (Line 519-558).

In addition to the considerations associated with interchangeability, BI would also highlight the fact that FDA has not yet decided how they will apply suffixes to the NPNs of interchangeable biologics or how the designation of interchangeability will be addressed via a product's label.

Suggestions for Improved Clarity

In the table below we outline other considerations for the Draft Guidance that require revision and/or clarification for clarity.

Page(s) / Line(s) in Draft Guidance	***Comments***	***Suggested Changes***
Page 6, lines 186-189 and 207-210	It is not clear how the fingerprint analysis could change the design of a clinical trial unless a certain outcome of a fingerprint analysis (plus biosimilar package information) could make the clinical study obsolete.	We suggest FDA explain in detail what is meant by "more selective and targeted."
Page 11, lines 420-425	Given that a sponsor will have conducted a PK/PD trial and possibly a confirmatory clinical trial comparing the biosimilar and reference product, a switching study aims to look for any differences in immunogenicity between staying on the reference product and switching between the reference and biosimilar. Therefore, a nearly complete wash-out of the reference for the last switch seems unnecessary. If at all, the last switch should be long enough to potentially capture any late immunogenic reaction.	We suggest FDA delete everything from ",where the … non –switching arm." (lines 421-425).

[13] FDA Draft Guidance, "Considerations in Demonstrating Interchangeability With a Reference Product", January 2017, available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf . Accessed February 20, 2017.

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Page(s) / Line(s) in Draft Guidance	***Comments***	***Suggested Changes***
Page 12, lines 438-440	The proposed 90% confidence interval (CI) between 80-125% as the sole acceptable outcome option of a multiple dose parallel design study is too restrictive and would require an unethically large number of subjects.	We suggest FDA allow sponsors to instead use the lead-in variability for scaling (as co-variate) and scale the ratio between the geometric mean parameters by the reference variability, allowing potentially wider 90% CI margins ("reference scaled"). We suggest FDA revise the text to read: "The 90% confidence interval for the geometric mean ratio of AUC_{tau} and C_{max} between the proposed interchangeable product and the reference product should be preferably within 80–125%. Wider 90% confidence interval margins may be acceptable based on the reference variability."
Page 12, lines 438-440	The guidance states that the "90% confidence interval for the geometric mean ratio of AUC_{tau} and C_{max} between the proposed interchangeable product and the reference product should be within 80-125%". Due to the proposed study design with a switching and a non-switching arm, we believe that the statement should instead refer to the geometric mean ratio between the switching arm and the non-switching arm rather than the proposed interchangeable product and the reference product.	We suggest FDA rephrase the sentence as follows: "The 90% confidence interval for the geometric mean ratio of AUC_{tau} and C_{max} between the switching and non-switching arm should be within 80-125%."

We applaud FDA for taking this step and issuing guidance on how to obtain an interchangeability designation. We believe that FDA should apply scientific and regulatory consistency to all biologics, including biosimilars and interchangeable biologics, to minimize any disruptive and disparate treatment of these products.

FDA plays a powerful role in ensuring that healthcare providers and patients have confidence in these products and understand that all biologics – biosimilar and interchangeable products included – are safe, pure and potent and all are manufactured by the required high quality standards for FDA approval and distribution to the US market. We encourage the Agency to avoid any unintended, inaccurate implications that interchangeable biologics are somehow "of higher quality" than not (yet) interchangeable designated biosimilars. We ask the Agency to consider our comments and suggestions, and we look forward to continuing to work with FDA to ensure a sustainable biosimilar marketplace.

Sincerely,

Palmisano,Dr.,Joann e (MED RA) BIP-US-R

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