



Boehringer Ingelheim
Pharmaceuticals Inc.

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

RE: Docket # FDA-2018-N-2689
Facilitating Competition and Innovation in the Biological Products
Marketplace; Public Hearing

September 21, 2018

Dear Sir or Madam:

Boehringer Ingelheim Pharmaceuticals, Inc. is pleased to submit comments on the Food and Drug Administration's ("FDA" or "the Agency") Part 15 Public Hearing "Facilitating Competition and Innovation in the Biological Products Marketplace," ("Proposed Rule") as published in the Federal Register on July 25, 2018¹. We incorporated all footnotes by reference into this docket, as well as our presentation at the Public Hearing itself².

Boehringer Ingelheim 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 welcomed FDA's invitation to comment at the public hearing and to provide further comments to the docket. We agree with the Agency that both competition and innovation will result from the Agency's successful implementation of the Biologics Price Competition and Innovation Act of 2009³ ("BPCIA") as enacted as Title VII of the Patient Protection and Affordable Care Act of 2010⁴ ("ACA"). Overall, we strongly support FDA's efforts to assist sponsors of biosimilars and interchangeable biologics to contribute to a competitive, multisource biologics market in the U.S., and we join FDA in working to achieve the goals most recently articulated in FDA's Biosimilar Action Plan⁵.

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¹ Proposed Rule: Facilitating Competition and Innovation in the Biological Products Marketplace; Public Hearing; Request for Comments. Federal Register Website, available at: <https://www.regulations.gov/document?D=FDA-2018-N-2689-0001>. Published July 25, 2018. Accessed September 16, 2018.

² Comments presented by Molly Burich for BI at Part 15 hearing on September 4, 2018

³ Biologics Price Competition and Innovation Act of 2009 (BPCIA), available at: <https://www.fda.gov/downloads/drugs/ucm216146.pdf>. Accessed September 19, 2018

⁴ Patient Protection and Affordable Care Act of 2010 (PPACA or ACA), available at: <https://www.congress.gov/111/plaws/publ148/PLAW-111publ148.pdf>. Accessed September 19, 2018

⁵ FDA Biosimilar Action Plan as issued July 18, 2018 and available <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm613761.pdf>

While we appreciate the FDA's efforts to date, we recognize that significant and immediate further action is needed to support the emergence of a genuinely competitive biologics market in the U.S. In addition to updating current regulatory approaches, the Agency needs to spearhead additional education for all stakeholders interested in the opportunities presented by FDA-approved biosimilars and interchangeable biologics.

As highlighted at the Part 15 Public Meeting, as well as more broadly⁶, misinformation abounds and the FDA's voice is needed for physicians and their patients to accurately access the opportunities offered by biosimilars and interchangeable biologics today and in the future. Only collectively, through the combined efforts of all stakeholders, from regulators to health care providers and payers, can we enhance access and affordability and thereby contribute to the broader FDA mission of protecting and promoting public health. It is clear that time is of the essence, given the apparent challenges from the launches of the first three biosimilars into the U.S. market. Absent changes to the current situation, we can expect the pipeline of biosimilars before the FDA to continue to be circumscribed and the prospects for competition in the U.S. to become further curtailed⁷.

Approved but not yet Marketed Biosimilars⁸

As the sponsor of an approved biosimilar, Boehringer Ingelheim recognizes the sizeable barriers to competition and access that biosimilars face in the U.S. specialty market. This includes barriers that extend well beyond their approval by FDA as a biosimilar and their designation by FDA as interchangeable. Nonetheless, Commissioner Gottlieb's statements earlier this year⁹ have helped highlight the very real challenges faced by sponsors when commercially launching a biosimilar in the U.S. (and have drawn useful parallels to the development of complex generics including lack of ready access to reference product). A new white paper titled "[Steps to Reducing Barriers to Biosimilars in the U.S.](#),"¹⁰ by Alex Brill and Christy Robinson of Matrix Global Advisors, echoes these challenges recognized by Commissioner Gottlieb and the Agency's recent report.

The emergence of a timely competitive and sustainable market for specialty medicines in the U.S. may be left uncertain unless solutions are found immediately. Hence throughout our comments Boehringer Ingelheim will convey a sense of urgency. We recognize that only some solutions can be implemented

⁶ Citizen petition from Pfizer, Inc. Available at: <https://www.regulations.gov/document?D=FDA-2018-P-3281-0001>. Accessed September 19, 2018

⁷ FDA Cumulative number of biosimilar development programs in the BPD Program in the month. Available at: <https://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=cder&status=public&id=CDER-RRDS-Number-of-biosimilar-dev-programs-in-BPD-Program&fy=All>. Accessed September 19, 2018

⁸ This section largely address Question 1 in the FDA Federal Register notice for the Part 15 meeting of September 4, 2018 <https://www.regulations.gov/document?D=FDA-2018-N-2689-0001>

⁹ Commissioner Gottlieb's speeches AHIP Capturing the Benefits of Competition for Patients, March 7, 2018 available at: <https://www.fda.gov/NewsEvents/Speeches/ucm599833.htm>; PCMA Advancing Patient Care Through Competition, April 19, 2018, available at: <https://www.fda.gov/NewsEvents/Speeches/ucm605143.htm> ; Keynote Address by Commissioner Gottlieb to the 2018 FDLI Annual Conference, May 3, 2018, available at: <https://www.fda.gov/NewsEvents/Speeches/ucm606541.htm>; Brookings Institution speech July 18, 2018, available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm613881.htm> and the video <https://www.brookings.edu/events/u-s-market-for-biosimilars-fda-scott-gottlieb/>.

¹⁰ Steps to Reducing Barriers to Biosimilars in the U.S.," by Alex Brill and Christy Robinson of Matrix Global Advisors

today by FDA, but we ask that those available to the Agency be acted upon immediately and are not delayed any further¹¹. Other solutions will require FDA leadership within HHS, as well as with other Agencies, and perhaps external to the U.S. Government, and can proceed in parallel.

We view the greatest barrier to launch to be the unnecessarily complex patent estates that have been created by reference product sponsors. The [Matrix White Paper](#) cites unjustified late-stage patents acquired by reference product companies with the goal of obstructing or delaying competition. To be clear, we strongly support legitimate intellectual property protections for true innovations as contemplated by the patent system and Boehringer Ingelheim has always supported the appropriate exclusivity for originator biologics as a fair trade for the right of reference to their prior approval¹², and as an appropriate way to encourage investment and market certainty for all biologic sponsors while also allowing for issuance of new patents for true innovations. But, we also believe that when that exclusivity is up, it is imperative for the system to allow for prompt market-based competition that can foster increased access and affordability for patients as well as stimulate the next generation of innovator products. This cannot currently occur in the U.S. With the average cost to develop a biosimilar at or above \$200 - \$300M; it is untenable to have multiple years of delays before being able to launch a product after clinical development and FDA approval. If this pattern continues, it is likely to have a significant impact on investment in future biosimilar development and that is even if we assume commercial success for all biosimilars once launched – currently far from a foregone conclusion¹³.

The patent provisions of BPCIA were intended to reduce the significant risk and uncertainties involved with ongoing litigation, much like Hatch Waxman¹⁴. The consequent delays are untenable to both biosimilar manufacturers as well as patients and the broader system that is increasingly in desperate need of the savings a robust biosimilar market can provide¹⁵.

¹¹ These include the acceptance of a global reference product as well as the minimization of unnecessary clinical studies – see proposal in Christopher J. Webster, Gillian R. Woollett (2017), “A ‘Global Reference’ Comparator for Biosimilar Development”. BioDrugs doi:10.1007/s40259-017-0227-4

<http://link.springer.com/article/10.1007%2Fs40259-017-0227-4>; and Christopher J. Webster, Gillian R. Woollett (2018) Comment <http://link.springer.com/article/10.1007/s40259-018-0297-y> on “The End of Phase 3 Clinical Trials in Biosimilars Development?” by Xavier Frapaise <https://doi.org/10.1007/s40259-018-0287-0>

¹² As previously articulated by Commissioner Gottlieb, “Helping Patients Benefit From Biotech Drugs” (2013). Available at: <https://www.forbes.com/sites/scottgottlieb/2013/09/30/helping-patients-benefit-from-biotech-drugs/#475e5d364335>. Accessed September 19, 2013

¹³ Remarks from FDA Commissioner Scott Gottlieb, M.D., as prepared for delivery at the Brookings Institution on the release of the FDA’s Biosimilars Action Plan. Available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm613881.htm>. Accessed September 19, 2018.

¹⁴ Hatch Waxman Drug Price Competition and Patent Term Restoration Act of 1984 available at <https://www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/STATUTE-98-Pg1585.pdf>. Accessed September 19, 2018. This Act already provided patent term restoration to biologics regulated under the PHA Act, but did not address exclusivity for biologics.

¹⁵ Fiona Scott Morton, Ariel Dora Stern, Scott Stern “The Impact of the Entry of Biosimilars: Evidence from Europe” Working paper. Available at: https://www.hbs.edu/faculty/Publication%20Files/16-141_4bf8cb85-55db-44c3-807d-d7467b0597f5.pdf. Accessed September 19, 2018

Improvements to the Purple Book¹⁶:

The FDA's Purple Book¹⁷ can be a valuable tool for all stakeholders, but it needs to contain additional accessible, current information to achieve its full potential as the primary resource for biosimilars. This is not just pharmacists, but also other healthcare providers, patients, payers and others whom we expect to trust FDA as the most accurate and timely resource on biosimilars and interchangeable biologics - just as they do for generics with the Orange Book¹⁸. To date the Purple Book contains very limited information compared to the Orange Book, and we believe that its value can be increased considerably.

By way of an important corollary, we also caution against inappropriate expectations for the Purple Book. We are concerned that some stakeholders may request changes to the Purple Book inconsistent with its purpose. For example, to describe what the listed products are not, rather than what they are. Any additions to the Purple Book that would list all biosimilars as "not interchangeable" is legally inaccurate and grossly misleading. It implies the biosimilar sponsor has asked FDA for an interchangeable designation and failed to obtain one. This will be wrong. It is *only* appropriate, as a legal matter, to list products in the Purple Book as biosimilars and interchangeable biologics – the two categories identified in BPCIA. And interchangeability should only ever be expected for those products where there is the opportunity for a pharmacist to substitute. Anything else raises concerns inappropriately and could easily create stakeholder confusion open to malevolent use.

At a time when the Agency recognizes the myriad misunderstandings surrounding biosimilars and interchangeable biologics and is taking action to educate the public¹⁹, we urge the Agency to be ever vigilant for additions to the Purple Book (or any other FDA messaging) that will serve to undermine the proven safety, efficacy, and quality of all FDA-licensed biosimilars, and that may impact confidence in FDA's oversight for all other biologics. That biosimilars are a form of biologics, and subject to the same regulatory requirements that apply to all biologics is not broadly understood – for example all CGMP requirements and establishment licenses to assure quality. We would also ask the Agency to add clear statements on FDA.gov to this effect.

Further, simple parallels to current Agency determinations can add the value of consistent messaging for those already involved in the practices of medicine and pharmacy. For example, as a legal matter an FDA designation of interchangeability for a biologics is equivalent to "therapeutic equivalence" and "A-rating" for generic small molecule drugs, with the authority for substitution by a pharmacist subject to state law in both instances. That "interchangeable biologics are not better biosimilars" also needs clear reiteration by the FDA. As the Agency is aware, interchangeable biologics are simply the same product,

¹⁶ This section largely address Question 2 in the FDA Federal Register notice for the Part 15 meeting of September 4, 2018 <https://www.regulations.gov/document?D=FDA-2018-N-2689-0001>

¹⁷ FDA's 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 September 19, 2018.

¹⁸ FDA's Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book). <https://www.fda.gov/drugs/informationondrugs/ucm129662.htm>. Accessed September 19, 2018.

¹⁹ FDA Biosimilars home page. Available at: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm>. Accessed September 19, 2018.

already determined by the FDA to be biosimilar to its reference biologic, upon which additional studies have been done²⁰. Such straightforward and clear messaging will help build physician confidence and understanding, while appropriately empowering pharmacists for those situations where their independent professional judgement is invited. Fairly managing expectations for all stakeholders is critical, and this must start with clarity as to the role of all health care professionals – physicians to prescribe and switch between originator biologics and biosimilars; pharmacists to substitute interchangeable biologics and dispense all medicines – in both instances subject to state law.

Another recommendation for the Purple Book, that we recognize would likely need statutory changes, would be to consider patent listings. As previously outlined, the number of patents held by reference product companies pose numerous challenges for biosimilar companies and we feel there is an opportunity for improvement using the Purple Book. We recommend that all process and product patents for a given reference product be listed in the manner already established by the Orange Book. This would help improve the efficiency of identifying which patents are relevant to the particular product, and save resources for all biologics sponsors, reference and biosimilar alike, better used for other purposes.

Interchangeability²¹:

Boehringer Ingelheim is the only company to have publicly announced the initiation of a clinical trial to demonstrate interchangeability for an FDA approved biosimilar²².

We believe the FDA outlined an appropriately high bar to establish interchangeability in the Draft Guidance “Considerations in Demonstrating Interchangeability with a Reference Product” issued January 2017²³. However, while we believe the bar to obtain an FDA-granted designation of interchangeability is and should be high, it must also be realistic and science-based in any regulatory requirements. While an appropriately high bar builds confidence in the interchangeable biologic pathway and is important to ensure these products achieve significant uptake in the market once they are available, its feasibility will govern whether and when any interchangeable biologics become available in the U.S. for American patients any time soon. For example, to facilitate the unique U.S. designation of interchangeability, we suggest FDA actively engage with other regulators to harmonize their regulatory approaches and in particular to consider appropriate criteria for a global reference product²⁴. We do not believe that U.S.-sourced reference product is always essential for those clinical studies conducted to support an FDA

²⁰ FDA draft guidance on IC, plus BI’s own comments to that docket

²¹ This section largely address Question 3 in the FDA Federal Register notice for the Part 15 meeting of September 4, 2018 <https://www.regulations.gov/document?D=FDA-2018-N-2689-0001>

²² <https://www.boehringer-ingelheim.us/press-release/boehringer-ingelheim-starts-clinical-study-interchangeability-between-its-adalimumab> July 2017

²³ 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 September 19, 2018.

²⁴ Christopher J. Webster, Gillian R. Woollett (2017), A ‘Global Reference’ Comparator for Biosimilar Development. BioDrugs doi:10.1007/s40259-017-0227-4. Available at <http://link.springer.com/article/10.1007%2Fs40259-017-0227-4>. Accessed September 19, 2018

designation of interchangeability²⁵, just as FDA has already concurred it is not for the initial approval of a biosimilar.

Also, additional studies to fulfill the statutory requirements of BPCIA should be carefully considered in terms of any questions that they may invite around the original biosimilar approval, not least given that FDA is routinely expecting transition studies from reference to biosimilar as part of the initial approval of the biosimilar. Indeed as Dr. Leah Christl clarified to a European audience earlier this year, FDA agrees with European regulators that biosimilars are already interchangeable with their reference *for the purposes of physicians' prescribing*²⁶. This was an extremely important statement and needs to be available on the FDA website to enable sponsors to explain that patients established on a reference product can be switched to the biosimilar – a point already established in the peer reviewed literature²⁷. This is a particular example of the critical role that FDA can play in the precise use of terminology – essential to the avoidance of misleading information to health care providers and consumers.

The Agency is already aware of some reference biologic sponsors' tactics to undermine a potential future designation of interchangeability by developing alternate formulations or other product variations that do not impact the fundamental components of the product and remain under the same Biologics License Application (BLA). Boehringer Ingelheim asserts that any changes within a single license are, by definition, acceptable variation within that single product's license²⁸, and as such represent acceptable variation for a biosimilar to that product. This must include a designation of interchangeability that is awarded to a biosimilar either before, or after, the originator gains approval of their variation using comparability to support their manufacturing change²⁹. To do otherwise would be to apply two different regulatorily disparate concepts to biosimilars/ interchangeable biologics from those historically applied to originator biologics. As such we implore the Agency to support the durability of the biosimilarity and interchangeability designation. The FDA can grant interchangeability to products as appropriately outlined in the draft guidance and sustain the designation against tactics that would seek to undermine competition by originator sponsors tweaking the reference product post approval. Interchangeability should be a designation that a given biosimilar should only need to attain

²⁵ BI comments to the FDA Draft Guidance "Considerations in Demonstrating Interchangeability With a Reference Product", January 2017. Available at: <https://www.regulations.gov/document?D=FDA-2017-D-0154-0019>. Accessed September 19, 2018.

²⁶ Medicine for Europe: 16th Biosimilar Medicines Conference – Biosimilar medicines: unlocking the full potential of biologics April 26-27, 2017 London. Available at: <https://www.medicinesforeurope.com/events/bios2018/>. Accessed September 19, 2018. Important to clarify that here interchangeable was not being used in the legal sense of meaning substitutable, but in terms of physician's being able to switch patients safely between biosimilars and their reference product.

²⁷ Hillel P. Cohen, Andrew Blauvelt, Robert M. Rifkin, Silvio Danese, Sameer B. Gokhale, Gillian Woollett (2018) "Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes", *Drugs*. Available at: <https://link.springer.com/article/10.1007/s40265-018-0881-y>. Accessed September 19, 2018

²⁸ Martin Schiestl, Thomas Stangler, Claudia Torella, Tadej Čepeljnik, Hansjörg Toll & Roger Grau. "Acceptable changes in quality attributes of glycosylated biopharmaceuticals" *Nature Biotechnology* 2011, Volume 29, Number 4. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21478841>. Accessed September 19, 2018

²⁹ FDA ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process, June 20015. Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073476.pdf> Accessed September 19, 2018

one time in their development – it is not something that should have to be chased based on anti-competitive action by the reference product manufacturer.

While the draft interchangeability guidance has been subject to much comment³⁰, and alluded to by Commissioner Gottlieb in recent speeches³¹, we ask FDA to finalize this guidance as soon as possible. We accept that, as with all FDA draft and final guidance, the Agency will always and should retain flexibility based on the nuances of a given product and the most appropriate requirements for that specific situation. However, in general, we support the draft guidance, and consider its availability in final form as soon as possible as a critical priority to fostering competition in the biologics specialty market in the U.S.

Continued FDA Activity to Address Market Challenges³²:

We support the excellent educational materials the Agency has developed and posted to the Agency's website³³. The marketplace is overflowing with misinformation and misleading messaging surrounding biosimilars and interchangeable biologics – a virtual torrent that has generated the perception of risk for patients switching to a biosimilar, even when specifically directed by their physician³⁴. FDA needs to assert its visibility as the primary source of accessible and reliable information suitable for health care providers and their patients, as well as product sponsors, sister Agencies (e.g. CMS and VA) and payers. But to do so, materials need to be prepared that are sensitive to the needs of the many audiences, and this will include those with less robust scientific and technical experience than the traditional biologic product sponsors. Others, such as professional societies and patient groups, can then be invited to help disseminate the Agency's accurate information reliably and more easily than if they have to prepare it for themselves.

That currently we have extensive misinformation swamping out the accurate material is harmful and likely constraining the therapeutic options for patients, and the expectations for biosimilars by their

³⁰ FDA's draft guidance Considerations in Demonstrating Interchangeability With a Reference Product docket. Available at: <https://www.regulations.gov/docket?D=FDA-2017-D-0154>. Accessed September 20, 2018

³¹ Scott Gottlieb speech at AHIP "Capturing the Benefits of Competition for Patients" on March 7, 2018. Available at <https://www.fda.gov/NewsEvents/Speeches/ucm599833.htm>. Accessed September 19, 2018; Remarks from FDA Commissioner Scott Gottlieb, M.D., as prepared for delivery at the Brookings Institution on the release of the FDA's Biosimilars Action Plan, July 18, 2018. Available at: <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm613881.htm>. Accessed September 19, 2018, plus FDA's Biosimilar Action Plan, Available at: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm613761.pdf>. Accessed September 19, 2018; Scott Gottlieb speech at Public Meeting on Facilitating Competition and Innovation in the Biological Products Marketplace, September 4, 2018. Available at: <https://www.fda.gov/NewsEvents/Speeches/ucm619277.htm>. Accessed September 19, 2018

³² This section largely address Question 9 in the FDA Federal Register notice for the Part 15 meeting of September 4, 2018 <https://www.regulations.gov/document?D=FDA-2018-N-2689-0001>

³³ FDA's Biosimilars website. Available at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm>. Accessed September 19, 2018

³⁴ Citizen petition from Pfizer, Inc. Available at: <https://www.regulations.gov/document?D=FDA-2018-P-3281-0001>. Accessed September 19, 2018

health care providers³⁵. However, the situation is further compounded by the fact that the misinformation is being applied disparately and specifically to biosimilars, and its relevance to all biologics lost, thereby fostering the erroneous impression that biosimilars are “more different” from their reference biologics, than those reference products are to themselves over time³⁶. It is not being applied to originator products undergoing manufacturing changes³⁷ because these changes are *de facto* invisible to patients and providers in the U.S.³⁸. FDA led the world with the concept of comparability in 1996³⁹, and this approach should not be undermined by irresponsible mis-portrayals of the power of analytics to define biologics. Indeed, better to recognize the need for science-based regulatory consistency for all biologics, and the confidence that the legitimate use of comparability has created in analytics for over two decades. If this can then be done globally, then such harmonization⁴⁰ can add to the efficiencies of manufacture for all biologics, for all sponsors, and thereby increase efficiency of appropriate regulatory oversight worldwide. This may allow the FDA to feed into the initiatives of others in a manner that can help those markets not traditionally recognized as highly regulated⁴¹, nor having as timely access to these important medicines as might now be possible through biosimilars. While we greatly appreciate FDA’s efforts to combat misinformation with its educational initiatives, we think there is an increased urgency to this effort and would like to recommend specific priorities. We suggest more specific initiatives that may reach beyond the Agency’s traditional audiences, such as downloadable brochures. Such primary sources are invaluable to a multiplicity of responsible stakeholders interested in ensuring biosimilars and interchangeable biologics can compete and provide

³⁵ Citizen petition from Pfizer, Inc. Available at: <https://www.regulations.gov/document?D=FDA-2018-P-3281-0001>. Accessed September 19, 2018

³⁶ Martin Schiestl, Thomas Stangler, Claudia Torella, Tadej Čepeljnik, Hansjörg Toll & Roger Grau. “Acceptable changes in quality attributes of glycosylated biopharmaceuticals” *Nature Biotechnology* 2011, Volume 29, Number 4. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21478841>. Accessed September 19, 2018

³⁷ FDA ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process, June 20015. Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073476.pdf> Accessed September 19, 2018

³⁸ The use of Comparability is public information in the EU.

Balázs Vezér, Zsuzsanna Buzás, Miklós Sebeszta & Zsombor Zrubka Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents 2016. Current Medical Research and Opinion, DOI: 10.1185/03007995.2016.1145579. Available at: <http://dx.doi.org/10.1185/03007995.2016.1145579>. Accessed September 19, 2018.

The same changes can be seen in US marketed product through analytical comparisons

³⁹ FDA Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products, April 1996. Available at: <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm>. Accessed September 19, 2018

⁴⁰ FDA Biosimilar Action Plan July 2018. Available at: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm613761.pdf>. Accessed September 19, 2018 . Page 3.

Actively exploring the potential for entering into new data sharing agreements with foreign regulators to facilitate the increased use of non-U.S.-licensed comparator products in certain studies to support a biosimilar application

⁴¹ WHO Prequalification of biosimilars - Guido Pantè, Copenhagen, September 2017. Available at: <https://extranet.who.int/prequal/sites/default/files/documents/Biosimilars%20pilot%20procedure.pdf>. Accessed September 19, 2018.

increased access and affordability to these essential medicines. They can also reach patients and providers who are at the “coal face” of commercial future for biosimilars. We fear that if the early biosimilars cannot gain market share in the U.S. in a fair and meaningful manner, then the pipeline of candidates at FDA will continue to decline⁴².

Beyond the immediate critical audiences, we have suggestions on additional content needed. We recommend the Agency provide succinct materials specifically aimed at switching/transitioning patients to biosimilars and interchangeable biologics, perhaps with materials specific to certain therapeutic areas such as immunology and oncology where the questions raised can be different. That biosimilars are not only appropriate for naïve patients but also for patients established on the reference needs to be conveyed with some urgency, if the first generation of biosimilars in the US are to lead the way for the next. A considerable part of the challenge with the uptake of even those biosimilars launched in the U.S. market is that physicians have been misled to expect a clinical change if current patients are switched. And yet the peer reviewed literature shows this to be a hypothetical concern⁴³. Meanwhile, there continues to be the proliferation of misleading terms across the landscape like “non-medical switching”. This does not apply to biosimilars as a scientific matter because clinically biosimilars are the same therapeutic protein as the originator and do not constitute a therapeutic switch for the patient. “Non-medical switching” is being actively used to dissuade physicians giving biosimilars to patients currently treated with the reference⁴⁴. These efforts extend to advocating for state legislation designed to block putative “nonmedical switching”, which would undermine FDA’s efforts to make biosimilars and interchangeable biologics available to patients. As such we would ask the Agency to specifically develop materials that can provide appropriate education and tools on patient transitions to biosimilars and interchangeable biologics for both healthcare professionals and patients alike. These can show how interchangeability is only to enable substitution by other than the prescriber, and is not relevant to any prescribing decision.

In conclusion, we reiterate that FDA plays a powerful role in ensuring that both 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 made to the same high quality standards. We encourage the Agency to avoid any unintended, inaccurate implications that interchangeable biologics are somehow “of higher quality” than not (yet) interchangeable designated biosimilars.

Boehringer Ingelheim applauds the FDA for holding this public meeting in order to draw attention to the need to foster competition for biologics in the US. We appreciate the opportunity to provide comments to the Agency and the continued support by the Agency for the biosimilar pathway. We believe that FDA

⁴² FDA Cumulative number of biosimilar development programs in the BPD Program in the month. Available at: <https://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=cder&status=public&id=CDER-RRDS-Number-of-biosimilar-dev-programs-in-BPD-Program&fy=All> Accessed September 19, 2018

⁴³ Hillel P. Cohen, Andrew Blauvelt, Robert M. Rifkin, Silvio Danese, Sameer B. Gokhale, Gillian Woollett (2018) Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes, Drugs. Available at: <https://link.springer.com/article/10.1007/s40265-018-0881-y>. Accessed September 19, 2018

⁴⁴ Citizen petition from Pfizer, Inc. Available at: <https://www.regulations.gov/document?D=FDA-2018-P-3281-0001>. Accessed September 19, 2018



should apply scientific and regulatory consistency to all biologics, including biosimilars and interchangeable biologics, to minimize any disruptive and disparate treatment of these products. We look forward to continued engagement on creating competition to allow a vibrant and sustainable U.S. biosimilar market.

Sincerely,

A handwritten signature in black ink that reads "Joanne Palmisano". The signature is fluid and cursive, with a long horizontal stroke at the end.

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