Mylan
Better Health for a Better World®

September 21, 2018

BY ELECTRONIC SUBMISSION

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2018-N-2689; Facilitating Competition and Innovation in the Biological Products Marketplace; Comments of Mylan, Inc.

Dear Sir or Madam:

Mylan Inc. ("Mylan") is pleased to provide written comments to the Food and Drug Administration ("FDA" or "the Agency") in response to the Agency's Part 15 public hearing and accompanying request for comments on "FDA's approach to enhancing competition and innovation in the biological products marketplace, including by facilitating greater availability of biosimilar and interchangeable products."[1] These written comments supplement Mylan's oral presentation at the public hearing on September 4, 2018.

Mylan is a global pharmaceutical company committed to setting new standards in healthcare. Mylan is the second largest provider of prescription medicine in the U.S. We seek to enhance access to high-quality, affordable medicines for patients worldwide. As part of that mission, Mylan is taking a leading role in the development of biosimilars and interchangeable biologics for the U.S. marketplace. Mylan's global product pipeline includes 20 biosimilar and insulin analog products, including eight of the world's top 10 biologics focused on the areas of oncology, immunology, endocrinology, and ophthalmology. Two of the twelve biosimilars approved by the U.S. FDA as of August 2018 are Mylan products. Mylan has a strong interest in ensuring that FDA's biosimilar-related policies are consistent with both patient safety and consumer access to affordable, high-quality medications.

Mylan commends FDA for recognizing the challenges facing the developing biosimilar market and soliciting input on how to facilitate competition and innovation so that biosimilars can deliver in the nascent biosimilar marketplace. While not new, these issues are particularly

[1] 83 Fed Reg. 35314, 35314 (July 25, 2018).

important given the current state of the biosimilar marketplace and the concerns over the accessibility and affordability of medicine and healthcare more generally in the U.S.

It is worth remembering that, when the Biologics Price Competition and Innovation Act ("BPCIA") became law in 2010, it was intended to balance reasonable protection for reference product manufacturers and accelerated development and marketing of biosimilars to improve the public health by delivering more affordable competition for products that had enjoyed monopolies for decades. To date, implementation of the BPCIA has produced a difficult environment for biosimilars and the patients who would benefit from the increased accessibility and affordability of these important treatments. In short, the current marketplace is protecting reference products from meaningful competition beyond what was intended. As FDA continues to implement the BPCIA, we ask that FDA bear in mind the current imbalance and strive to correct it. We hope that this public hearing process and our comments can help resolve any outstanding issues and lead to final guidance and other agency action to realize a robust and competitive biosimilar marketplace in the interest of promoting the public health through increased access to these life-changing treatments, and most importantly benefit to patients.

As Commissioner Gottlieb has noted, other agencies also play a role in determining the extent to which biosimilars are available to and accepted by patients and the healthcare establishment.[2] Those other agencies certainly need to do their part, and FDA has a role to play in partnering with those agencies to realize the full potential of biosimilars, however, we have focused our comments on the following issues identified through the public hearing process, all of which are within FDA's jurisdiction:

- FDA's role in providing education for patients, providers, and payors, including combatting misinformation
- Interchangeability
- General approval and post-approval issues
- Use of non-U.S. reference product
- Treatment of transitional biologics
- Exclusivity for reference products
- Non-proprietary naming

Notably, many of the issues have also been raised in other biosimilar dockets, including a public meeting convened by FDA in 2010 soon after the BPCIA became law.[3] Rather than reiterate the detailed analyses and explanations that have been previously provided to the Agency, Mylan

[2] *See* Gottlieb, *Capturing the Benefits of Competition for Patients*, *available at* https://www.fda.gov/NewsEvents/Speeches/ucm599833.htm (explaining some of the non-FDA related barriers to competition in the biosimilars market, including federal policies as well as reference drug commercial and contracting approaches).
[3] 75 Fed. Reg. 61497 (Oct. 5, 2010).

asks FDA to incorporate those comments by reference.[4] Mylan is also a member of the Association for Accessible Medicines ("AAM") and endorses its comments to this and related dockets.

I. FDA's Role in Providing Education for Patients, Providers, and Payors, including Combatting Misinformation

Mylan agrees with the weight of opinion at the hearing and with the currently-pending Pfizer citizen petition[5] that there is misunderstanding among payors, providers, and patients regarding the nature and performance of biosimilars. For instance, there is a lack of understanding that biosimilars have been found to have the same clinical effect and safety profile as the reference drug for its approved uses – a foundational finding that is inherent in FDA's approval of a biosimilar. We believe that this, and other misunderstandings, are contributing to the slower than expected uptake of new biosimilars – even where the biosimilar offers a price advantage over the reference drug.

We know that FDA is aware of this issue. Dr. Gottlieb expressed his understanding of the problem cogently, when he noted last March that "physician and patient confidence in the quality and safety of biosimilar products is critical to their market acceptance. And at FDA, we want to address any misconceptions or concerns that may be out there."[6] We acknowledge that FDA has undertaken several educational outreach programs, such as the October 2017 Biosimilars Education Campaign,[7] and that FDA has also promised more educational activities in its Biosimilars Action Plan,[8] which includes a plan to provide a one-pager for patient audiences and

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[4] Mylan Comment to *Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing*, Docket No. FDA-2010-N-0477-0057 (Dec. 30, 2010); Mylan Comment to *Options for a User Fee Program for Biosimilar Product Applications for Fiscal Years 2013 through 2017*, Docket No. FDA-2011-N-0326-0021 (June 10, 2011); Mylan Combined Comment to *Draft Guidance on Scientific Considerations in Demonstrating Biosimilarity to Reference Product*, *Draft Guidance for Industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, and *Draft Guidance on Quality Considerations in Demonstrating Biosimilarity to a Reference Product*, Docket No. FDA-2011-D-0605-0039 (Apr. 16, 2012); Mylan Comment to *Draft Guidance on Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the Public Health Service Act*, Docket No. FDA-2013-D-1165-0016 (Oct. 30, 2014); Mylan Comment to *Draft Guidance on Nonproprietary Naming of Biological Products*, Docket No. FDA-2013-D-1543-0179 (Nov. 13, 2015); Mylan Comment to *Draft Guidance on Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of* 2009, Docket No. FDA-2015-D-4750-0007 (May 18, 2016)).

[5] Pfizer Citizen Petition, Docket No. FDA-2018-P-3281 (Aug. 22, 2018).

[6] *See* Gottlieb, *Capturing the Benefits of Competition for Patients*, *available at* https://www.fda.gov/NewsEvents/Speechesucm599833.htm.

[7] *See* Scott Gottlieb & Leah Christl, "FDA Taking New Steps to Better Inform Physicians about Biosimilars Through Education about these Potentially Cost-Saving Options," FDA Voice (Oct. 23, 2017), https://blogs.fda.gov/fdavoice/index.php/2017/10/fda-taking-new-steps-to-better-inform-physicians-about-biosimilars-through-education-about-these-potentially-cost-saving-options/.

[8] Biosimilars Action Plan: Balancing Innovation and Competition (July 2018), *available at* https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm613761.pdf.

videos for healthcare professionals that explain key concepts about biosimilarity and interchangeability. These additional efforts to educate healthcare professionals and patients will be helpful, but we believe even more is needed and that FDA is uniquely situated to credibly address misinformation and half-truths that create barriers to the uptake of biosimilars.

We request that FDA continue to help educate all participants in the health care system, including payors, providers, and patients, including patient advocacy groups, about biosimilars and interchangeable products. Moreover, we ask that FDA disseminate its educational materials broadly, including in downloadable forms that can be shared with the various stakeholders. For instance, FDA should draft patient brochures on biosimilars that a health care professional could download, print, and provide to a patient. FDA should also consider efforts to educate via medical journals as well as the lay press.

To target specific misunderstandings of which we are aware, we suggest that FDA stress the following messages:

- Biosimilars have the same clinical effect as the reference drug, and there is no reason not to prescribe the less expensive biosimilar to patients who have previously not taken any drug for their condition.
- Transitioning a patient from a reference drug to a biosimilar is acceptable regardless of whether the drugs have been determined to be interchangeable. Interchangeability is a designation awarded by FDA that is intended to permit substitution at the pharmacy level, which is different than a supervised transition among products, which occurs regularly in the practice of medicine for various reasons, including cost. A transition, or switch, from a reference biologic to an FDA-approved biosimilar will not result in any clinical difference in the patient's treatment, and studies show that transitioning a patient to a biosimilar does not result in increased adverse events.[9]
- Transitioning between biosimilars that reference the same originator product is, as a scientific matter, not anticipated to result in any clinical difference in a patient's treatment.
- Quality requirements for biosimilars are the same as quality requirements for reference drugs.
- An interchangeable biologic is not a "better" biosimilar, it is a biosimilar for which additional data has been provided to meet a statutory definition related to automatic pharmacy substitution.

[9] *See* Cohen, H.P., Blauvelt, A., Rifkin, R.M., et al., *Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes*, Drugs 78:463-78 (2018); Moots R., Azevedo V., Coundreau, J.L., et al., *Switching Between Reference Biologics and Biosimilars for the Treatment of Rheumatology, Gastroenterology, and Dermatology Inflammatory Conditions: Considerations for the Clinician*, Curr. Rheumatol. Rep. 19:37-53 (2017).

- A biosimilar is as similar to the reference biologic as batches of the reference biologic are to each other. The same concept of comparability used as the foundation of a biosimilarity assessment is also used when assessing originator biologic products following manufacturing changes.

Further, we support any Agency guidance that would help to prevent false and misleading statements, as recommended in the Pfizer citizen petition.[10] We also request that FDA take enforcement action against false and misleading statements regarding biosimilars made by brand companies determined to disseminate misinformation and create barriers to the uptake of biosimilars.

II. Interchangeability

It has been over eight years since the BPCIA became law, and there are still no approved interchangeable products. Until FDA finds a workable pathway to the development and expeditious approval of interchangeable biological products, the full benefits of biosimilars to the overall healthcare system will not be realized. We agree with AAM's comment to FDA's draft interchangeability guidance[11] that FDA's draft guidance relied on unnecessarily complex and costly multi-switch clinical trials in U.S. patients to demonstrate interchangeability.[12] Moreover, we applaud Commissioner Gottlieb's interest in "updating the guidance on interchangeability and trying to see about how we can create a lower hurdle for companies demonstrating interchangeability."[13] A less burdensome approach makes perfect sense based on the scientific approach to biosimilarity. As a scientific matter, the core concept of biosimilarity – comparability or high similarity – is well established in the context of manufacturing changes made to reference products. Notably, once established as comparable, pre-change and post-change reference product are treated as interchangeable.[14] Moreover, as the science of analytics and comparability continue to advance, the evidence continues to support these methods as highly sensitive and uniquely capable of identifying and examining very small differences between molecules.

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[10] *See* Pfizer Citizen Petition, Docket No. FDA-2018-P-3281 (Aug. 22, 2018), at 10-11.
[11] Draft Guidance, *Considerations in Demonstrating Interchangeability With a Reference Product* (Jan. 2017).
[12] AAM Comment to *Draft Guidance on Considerations in Demonstrating Interchangeability with a Reference Product*, Docket No. FDA-2017-D-0154-0028 (May 19, 2017) at 3, 9-10.
[13] Cathy Kelly, "US FDA Biosimilar Guidance Update Will Relax Interchangeability Standards," Pink Sheet (Apr. 21, 2018), https://pink.pharmaintelligence.informa.com/PS122952/US-FDA-Biosimilar-Guidance-Update-Will-Relax-Interchangeability-Standards.
[14] *See* Webster, C.J. and Woollett, G.R., *A 'Global Reference' Comparator for Biosimilar Development*, BioDrugs 31:279-86 (2017).

III. General Approval and Post-Approval Issues

Mylan requests that FDA continue to examine its approach to biosimilar development programs more generally to be sure that they are efficient in terms of meeting the robust scientific standards for approval. We urge FDA to maintain a flexible approach that takes into account the particulars of the product and the program such that the sponsor and FDA can, for instance, refine the use of statistical tools and tailor the numbers and types of lots used in development.

Moreover, in terms of approving changes related to developing commercial scale capacity, Mylan encourages FDA to work with the biosimilar industry to enable rapid post-approval scale-up and site transfer, including a flexible approach to scientifically justified reductions in stability programs for drug substance and drug product as part of its efforts to maximize patient access to these important treatment options. In considering post-approval manufacturing changes for biosimilars and interchangeable biologics generally, Mylan encourages FDA to ensure comparability remains at the core, and standards do not exceed those required of originator biologic manufacturers.

IV. Use of Non-U.S. Reference Products

FDA has taken some steps to allow use of a non-U.S. licensed comparator product in certain studies to demonstrate that the proposed biological product is biosimilar to the U.S.-licensed product.[15] Of particular concern, however, is the number and nature of studies that must be conducted to use a non-U.S. reference drug. Currently, to rely on an animal or clinical study using a non-U.S.-licensed comparator, sponsors must submit analytical and clinical bridging studies between the biosimilar, the non-U.S.-licensed reference product used in development of the biosimilar, and the U.S.-licensed product.

These bridging studies are expensive, contribute little to the science, and unnecessarily expose patients to investigational products. As Commissioner Gottlieb noted, "We're literally exposing patients to drugs in a clinical trial just because we can't acknowledge something we know. We're going to see whether or not there are ways we can acknowledge that knowledge."[16] FDA has pledged to explore eliminating the requirement for such bridging studies and exploring new data sharing agreements with foreign regulators as a potential way to address these issues.[17] Mylan supports this work and believes that a more streamlined process making use of a global

[15] Final Guidance, *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (Apr. 2015) at 8-10; Draft Guidance, *Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (May 2015) at 11-12.

[16] Sue Sutter, "Biosimilar Bridging Study Waivers: Public Health Prerogative Or Trade Secret 'Taking'?," Pink Sheet (Sept. 10, 2018), https://pink.pharmaintelligence.informa.com/PS123843/Biosimilar-Bridging-Study-Waivers-Public-Health-Prerogative-Or-Trade-Secret-Taking.

[17] Biosimilars Action Plan: Balancing Innovation and Competition (July 2018) at 3.

comparator product is not only possible but is also critically important to ensuring the viability of the biosimilar marketplace. Accordingly, we encourage FDA to waive bridging studies and also consider global comparator product qualification along the lines laid out in the IGPA position paper "Reflection Paper on Waiving Bridging Studies for Biosimilar Medicines Applications," which outlines circumstances where bridging studies between local and foreign reference product may reasonably be waived based on scientific and regulatory principles such as active ingredient and product composition, data relied on for approval, and application of ICH Q5E principles to any manufacturing changes since approval.[18] After all, originator biologics are able to pursue global development plans – this is clear (and public) when examining the clinical studies relied on for approval in the various jurisdictions[19] – it seems fair that biosimilar sponsors should be able to, too.

V. Treatment of Transitional Biologics

The BPCIA provides that, on March 23, 2020, a number of biological products that, for historical reasons, are currently regulated as drugs will be "deemed" licensed biologics under the Public Health Service Act ("PHSA").[20] In the draft guidance, FDA has interpreted the language in the BPCIA to require that any pending application for a "transitional biologic" that does not receive final approval by the March 23, 2020 transition date must be resubmitted as biologic application.[21] As discussed in our comment to the draft guidance,[22] FDA's current interpretation not only conflicts with the language and structure of the BPCIA, it will cause severe disruption to the development programs and application processes for transitional biologics, which undermines the purpose of the law. Even FDA concedes in its draft guidance that its policy "could have a significant impact on development programs for any proposed protein products intended for submission under section 505 of the FD&C Act that are not able to receive final approval by March 23, 2020."[23]

There is precedent for FDA to handle the transition in a way that honors the language of the BPCIA, which expressly permits sponsors of transitional biologics to submit applications under the drug provisions of the Federal Food Drug and Cosmetic Act ("FDCA") until March 23, 2020,

[18] IGBA, Reflection Paper on Waiving Bridging Studies for Biosimilar Medicines Applications (Sept. 13, 2018).
[19] *See* Webster, C.J. and Woollett, G.R., *A 'Global Reference' Comparator for Biosimilar Development*, BioDrugs 31:279-86 (2017).
[20] Biological Price Competition and Innovation Act, section 7002(e).
[21] Draft Guidance, *Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009* (Mar. 2016).
[22] Mylan Comment to *Draft Guidance on Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act*, Docket No. FDA-2015-D-4750-0007 (May 13, 2016).
[23] Draft Guidance, *Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act* (Mar. 2015) at 5.

and does not require the disrupting resubmission of these applications.[24] Put simply, FDA should follow this precedent and the language and intent of the BPCIA to provide a seamless transition for the product under review by permitting a pending 505(b)(2) application to simply continue its review until approval and, upon approval, deem the approved product to be a licensed biologic consistent with its authority.

When it comes to transitioning already approved transitional biologics that have been approved under 505(b)(2) of the FDCA, we agree with AAM's comment[25] that FDA should not adopt the one-size fits all approach of transitioning all 505(b)(2)s to be licensed 351(a) applications under the PHSA advocated by Eli Lilly and Company,[26] but rather should consider the nature of the 505(b)(2) and work with the sponsor to determine how they intend for their biologic to exist in the marketplace. Some sponsors may intend for their product to be simply another brand biologic, but others may want to increase access and affordability by competing in the market as biosimilars or interchangeable products licensed under 351(k).

VI. Exclusivity for Reference Products

FDA requested comment on whether FDA should grant "umbrella exclusivity" to reference products after a change has been made to the product.[27] Under an umbrella policy, changes to a reference product that would not give rise to a new exclusivity period would be protected by whatever time remains of the original exclusivity period. We believe the BPCIA forecloses umbrella exclusivity. The statute explicitly states that the 4- and 12- year exclusivity periods covering the reference product "shall not apply" to (a) an approved supplement, or (b) an approved BLA for a new indication, route of administration, dosing schedule, dosage form, delivery system, deliver device, or strength.[28] This language erects bars not only to the award of a new exclusivity period to biological products with non-structural modifications, but also to the application of the original exclusivity period covering the reference product to a modified product under an umbrella policy. Because the statutory language is clear and unambiguous, it evinces a clear Congressional repudiation of FDA's umbrella policy in the context of reference product exclusivity under the BPCIA. AAM's comments to this docket provide additional analysis of the meaning of the statute, with which we agree.

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[24] *See* Mylan Comment, Docket No. FDA-2015-D-4750-0007 at 14-17; AAM Comment to *Draft Guidance on Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act*, Docket No. FDA-2015-D-4750-0010 (May 13, 2016) at 7-9.
[25] AAM Comment to *Draft Guidance on Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act*, Docket No. FDA-2015-D-4750-0018 (May 31, 2018).
[26] Eli Lilly and Company Comment to *Draft Guidance on Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act*, Docket No. FDA-2015-D-4750-0015 (Dec. 4, 2017).
[27] 83 Fed. Reg. 35154, 35156 (July 25, 2018).
[28] 42 U.S.C. § 262(k)(7)(C).

In addition to following the language and structure of the BPCIA to foreclose any application of "umbrella exclusivity," FDA should make timely, transparent designations of reference product exclusivity and make both the determination, and the rationale for the determination, public. FDA has said that it will make an exclusivity decision for reasons of regulatory necessity or at the request of the license holder.[29] In our view, this is not sufficient. FDA needs to make these determinations on its own initiative, or, at the very least, on the request of any person and publish in the Purple Book all of the determinations it has made, together with the date that any remaining exclusivity will expire.

This information is important to potential biosimilar sponsors who may be considering whether and when to develop a potential biosimilar competitor to the reference product. Many of these determinations will be straightforward because the product and any substantial changes will have been made more than 12 years ago. Even where a determination may require some effort on the part of the Agency, however, we believe the effort is worth it to provide clarity to potential biosimilar sponsors. For new reference drug biologic approvals and supplements, for instance, FDA should make exclusivity determinations at the time of approval, and publish those determinations in the Purple Book immediately.

VII. Non-proprietary Naming

For the reasons discussed in Mylan's prior comment, Mylan views FDA's current non-proprietary naming convention for biological products to be unnecessary for pharmacovigilance purposes and harmful to the uptake of biosimilars.[30] As described in FDA's final guidance, both the reference products and biosimilars are intended to have the same core name with each product having different four-letter meaningless suffixes.[31] However, as a practical matter, all of the biosimilars approved to date involved reference drugs that were named before this policy was adopted, and all the approved biosimilars were approved after the policy was adopted. This means that no reference product for which there is an approved biosimilar carries a suffix and so biosimilars are distinguished from their reference products through these suffixes.

This hinders the uptake of biosimilars, with the difference in names suggesting that there are differences between a biosimilar product that carries a suffix and the reference product without. This misimpression undermines FDA's finding that the reference drug and the biosimilar have the same clinical effect and safety profile. Reference drug companies have tried hard to

[29] Background Information: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations (Purple Book), *available at* https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411424.htm.
[30] Mylan Comment to *Draft Guidance on Nonproprietary Naming of Biological Products*, Docket No. FDA-2013-D-1543-0179 (Nov. 12, 2015) at 2-3, 8-11, 16-17.
[31] Final Guidance, *Nonproprietary Naming of Biological Products* (Jan. 2017) at 1.

reinforce this erroneous perception. The Pfizer petition, for example, discusses a situation in which a reference drug company markets its biologic on the web with the words: "See what you're missing without the suffix,"[32] in an effort to create unwarranted distinctions based on the established name suffix carried by the biosimilar, and illustrates precisely the point made by the biosimilars industry and the FTC in urging FDA to retain the naming system that is both familiar to stakeholders and has proven more than sufficient for pharmacovigilance purposes.[33]

Mylan requests that FDA eliminate the suffixes. If FDA is unwilling to do so, however, we ask that FDA move expeditiously to help level the playing field by ensuring that all reference drugs also carry suffixes. Reference product sponsors do not seem to be supplementing their BLAs to add suffixes, but FDA has generated suffixes for new biologics recently approved under section 351(a), including Hemlibra (emicizumab-kxwh), Mepsevii (vestronidase alfa-vjbk), and Luxturna (voretigene neparvovec-rzyl), and we see no reason why FDA cannot do the same for reference product biologics previously approved under 351(a).[34]

VIII. Conclusion

Mylan appreciates FDA's efforts, through its Biosimilar Action Plan and ongoing implementation of the BPCIA, to understand how it can ensure a robust biosimilar marketplace. We hope that our comments will assist FDA as it refines its approach to these key issues in a way that delivers on the promise of biosimilars to improve patient access to these important life-changing treatment options.

Sincerely,

Arnd Annweiler
Head of Global Biologics, Mylan

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[32] Pfizer Citizen Petition, Docket No. FDA-2018-P-3281 (Aug. 22, 2018) at 7.
[33] *See* FTC Comment to *Draft Guidance on Nonproprietary Naming of Biological Products*, Docket No. FDA-2013-D-1543-0146 (Oct. 27, 2015) at 2, 7-9; AAM Comment to *Draft Guidance on Nonproprietary Naming of Biological Products*, Docket No. FDA-2013-D-1543-0141 (Oct. 27, 2015) at 2.
[34] *See* BLA 761083 Approval Letter to Genentech, Inc. for Hemlibra (emicizumab-kxwh) (Nov. 16, 2017), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/761083Orig1s000ltr.pdf; BLA 761047 Approval Letter to Ultragenyx Pharmaceutical, Inc. for Mepsevii (vestronidase alfa-vjbk) (Nov. 15, 2017) *available at* https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/761047Orig1s000ltr.pdf; BLA 125610 Approval Letter to Spark Therapeutics, Inc. for Luxturna (voretigene neparvovec-rzyl) (Dec. 19, 2017), *available at* https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM589690.pdf.