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

Re: Draft Guidance on Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009 (Docket No. FDA-2015-D-4750)

Dear Sir or Madam:

On March 14, 2016, the Food and Drug Administration (FDA) issued a notice seeking comments on its draft guidance entitled "Implementation of the 'Deemed to be a License' Provision of the Biologics Price Competition and Innovation Act of 2009" (the 2016 Draft Guidance). The 2016 Draft Guidance describes FDA's approach to implementation of the statutory provision in section 7002(e) of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) under which an application for a biological product approved under section 505 the Federal Food, Drug, and Cosmetic Act (FD&C Act) on or before March 23, 2020, will be "deemed to be a license" for the biological product under section 351 of the Public Health Service Act (PHS Act) on March 23, 2020.

Our firm represents numerous sponsors, applicants, and manufacturers who have developed biological products that are approved either under the FD&C Act or the PHS Act. Our firm also represents numerous sponsors and applicants that have successfully used the 505(b)(2) approval pathway under the FD&C Act, including for applications for biological products. Among our clients are sponsors of biological products who intend to submit applications for products under section 505(b)(2) of the FD&C Act prior to March 23, 2020, and who do not have control over whether these applications will receive final approval on or before March 23, 2020.

I. BACKGROUND

In accordance with previous FDA policies, regulations, and interpretations, sponsors have historically submitted marketing applications for certain biological products (e.g., protein products) under section 505 of the FD&C Act rather than under section 351 of the PHS Act. As such, these applications (i.e., NDAs) are subject to the conditions of approval for new drugs set forth under the FD&C Act, including the potential for applications under sections 505(j) or 505(b)(2) to reference them as listed drugs and rely on the agency's previous finding of safety and efficacy for those drugs to support approval. On March 23, 2010, the BPCI Act was enacted as part of the Patient Protection and Affordable Care Act (Publ. L. No. 111-148, 124 Stat. 119). Among other things, the BPCI Act requires that a marketing application for a "biological product" be submitted under section 351 of the PHS Act, subject to certain exceptions during the 10-year transition period ending on March 23, 2020. BPCI Act § 7002(e)(1)-(3) and (e)(5). In addition, under the BPCI Act, on March 23, 2020, an approved application for a biological product under section 505 of the FD&C Act shall be "deemed to be a license" for the biological product under section 351 of the PHS Act. *Id.* § 7002(e)(4). The BPCI Act is silent as to how FDA is to handle approval of applications for biological products submitted under section 505 of the FD&C Act that have been submitted, but not yet approved, as of March 23, 2020.

On March 14, 2016, FDA issued the 2016 Draft Guidance, describing a proposed approach to implementation of these provisions of the BPCI Act. We believe the 2016 Draft Guidance includes an unnecessarily restrictive proposal for handling applications for biological products submitted under section 505 of the FD&C Act that have been submitted but not yet approved as of March 23, 2020. This comment focuses on FDA's proposed treatment of such applications. We hope to show that the relevant provisions of the 2016 Draft Guidance are overly burdensome on sponsors and applicants of new applications, create an unnecessary period during which no abbreviated path for competition exists, and serve to undermine the public health mission of FDA.

II. OVERVIEW OF BPCI ACT PROVISIONS

The BPCI Act amended the PHS Act and other statutes to create an abbreviated licensure pathway for biological products shown to be biosimilar to, or interchangeable with, a licensed biological reference product. BPCI Act §§ 7001-7003. As FDA acknowledges in the 2016 Draft Guidance, the objectives of the BPCI Act are conceptually similar to those of the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly referred to as the "Hatch-Waxman Act"), which recognized the public health benefit of avoiding duplicate research and established abbreviated pathways for the

approval of drug products under section 505(b)(2) and 505(j) of the FD&C Act. Pub. L. 98-417. Three provisions of the BPCI Act are germane to this comment.

First, like the Hatch-Waxman Act, the BPCI Act includes periods of exclusivity for biological products licensed under section 351 of the PHS Act, including a 12-year period from "the date on which the reference product was first licensed" during which approval of a 351(k) application referencing that product may not be made effective. PHS Act § 351(k)(7).

Second, the BPCI Act requires marketing applications for biological products to be submitted under section 351 of the PHS Act, subject to a limited exception during a 10-year transition period ending on March 23, 2020. BPCI Act § 7000(e). During this transition period, a biological product in a product class in which another biological is approved under an NDA "may be submitted under section 505 of the [FD&C Act]," if there is not another biological product licensed under section 351(a) of the PHS Act that could be a reference product with respect to such application. *Id.*

And third, an approved application for a biological product under section 505 of the FD&C Act "shall be deemed to be a license for the biological product under [section 351(a) of the PHS Act] on the date that is 10 years after the date of enactment…" (i.e., March 23, 2020). *Id.* § 7000(e)(4).

The interplay of these three provisions has a dramatic impact on the ramifications of FDA's interpretation of the "deemed to be a license" language.

III. FDA'S INTERPRETATION OF THE "DEEMED TO BE A LICENSE" PROVISION CONFLICTS WITH POLICY GOALS OF STATUTE, AND CREATES UNINTENDED CONSEQUENCES FOR CURRENT SPONSORS

The focus of the 2016 Draft Guidance is on the implementation of section 7000(e)(4) of the BPCI Act, referred to as the "deemed to be a license" provision, that takes effect at the end of the 10-year transition period on March 23, 2020. As noted above, the language of the BPCI Act provides only that NDAs for biological products will be deemed to be a 351(a) license, or BLA, on March 23, 2020. FDA interprets this provision to mean that, on March 23, 2020, "applications for biological products that have been approved under section 505 of the FD&C Act will no longer exist as New Drug Applications (NDAs) (or, as applicable, Abbreviated New Drug Applications (ANDAs)) and will be replaced by approved Biologics License Applications (BLAs) under section 351(a) or 351(k) of the

PHS Act, as appropriate." 2016 Draft Guidance at 5 (emphasis added). FDA then goes further, interpreting the provision to mean that "the Agency will not approve any application under section 505 of the FD&C Act for a biological product...that is pending or tentatively approved 'on' March 23, 2020, even though section 7002(e)(2) of the BPCI Act expressly permits submission of an application under section 505 of the FD&C Act 'not later than' March 23, 2020..." *Id.* As a further result of these interpretations and extensions of the statutory language, the Agency intends to remove products that are deemed to have licenses as "listed drugs" in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) on March 23, 2020. As of that date, therefore, FDA's findings of safety and effectiveness for such products may not be relied upon by a 505(b)(2) applicant for approval of a related product, even if that product's NDA is under active review at the time. *Id.* at 6.

Although FDA recognizes that its interpretation will 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," its recommendations to mitigate this impact are unrealistic and, therefore, overly burdensome. *Id.* For instance, FDA recommends that sponsors of development programs for proposed biological products "should evaluate whether a planned submission under section 505 of the FD&C Act would allow adequate time for approval of the NDA..., considering, among other things, whether the submission may require a second cycle of review..." *Id.* at 7. This recommendation is unrealistic in that sponsors submit applications that they believe are complete and able to be approved. NDA applicants are notoriously unable to accurately predict the time needed for approval as numerous issues which may be unanticipated by both the sponsor and FDA prior to submission of the application often result from FDA review. What a sponsor can reasonably predict, however, is the time to submission. This aligns with the statutory language of the BPCI Act, which sets out that sponsors may submit these applications under section 505 of the FD&C up until March 23, 2020. BPCI Act § 7002(e). FDA's interpretation leaves affected biological product sponsors unable to effectively plan for a 505(b)(2) application. Most often, the affected products are improvements on the underlying listed drug that are economically viable only if the applicant is not required to replicate all relevant studies for the listed drug. As such, these sponsors would be unlikely to invest the additional resources needed to submit a full 351(a) BLA. Assuming that current development timelines for these drugs project a 505(b)(2) submission date prior to March 23, 2020, their sponsors must make a decision regarding continued development of their products (including expenditure of significant investment dollars) based solely on issues outside of their control – that is, the date on which the NDA would be approved.

An additional unintended, and perhaps unrecognized, consequence of FDA's interpretation is the establishment of a period during which, for classes of biological products subject to the transition provision, no form of abbreviated application can be submitted. This is because no biological product would be approved under section 351(a) of the PHS Act to serve as the reference product for an application under section 351(k) of the PHS Act, and as of May 2019 (and likely much earlier) it would be too late to submit a 505(b)(2) application without running up against FDA's deadline for approving such applications. This is contrary to the objectives of both the Hatch-Waxman Act and the BPCI Act, which are intended to establish abbreviated pathways for the approval of follow-ons to FDA-approved products and to enhance competition. Instead, FDA's interpretation that it will not review pending 505(b)(2) applications for biological products after March 23, 2020 unnecessarily limits an existing avenue for competition. The result is the potential for a monetary windfall to sponsors of biological product NDAs that serve as listed drugs able to be referenced in 505(b)(2) applications.

While the BPCI Act does not explicitly provide a basis for FDA to continue to recognize approved NDAs for biological products after such applications are deemed to be BLAs on March 23, 2020, the BPCI Act also does not forbid it for the limited time needed to allow submitted 505(b)(2) applications to be reviewed and approved. Implementation of this alternative interpretation of the "deemed to be a license" provision of the BPCI Act (discussed more fully below) would cure the issues discussed above. We recognize that it would also establish a short period of duality during which products that serve as listed drugs in an already submitted 505(b)(2) NDA would continue to exist as listed drugs while also being licensed under section 351(a) of the PHS Act. Any administrative burden created by this duality can not outweigh the very real and significant economic burden imposed by implementation of the interpretation in the 2016 Draft Guidance.

IV. AN ALTERNATIVE STATUTORY READING MORE APPROPRIATELY WEIGHS BURDENS ON CURRENT DEVELOPMENT PROGRAMS

The BPCI Act explicitly states that an application for approval of certain biological products may be *submitted* as an NDA not later than March 23, 2020. BPCI Act § 7002(e)(2)(B)(ii). Rules of statutory construction suggest that Congress would not have provided for submission of an NDA as late as March 22, 2020 if that application would not be approvable the next day because FDA was not authorized to review or approve it. Consistent with this reading, FDA should interpret the "deemed to be a license" provision to allow continued review of already submitted NDAs and to permit continued reliance on a listed drug even after that drug's NDA is deemed to be a license.

Under this reading of the statute, applications submitted by March 23, 2020 would be eligible for review and approval under section 505 of the FD&C Act and, subsequently, deemed to be a license under section 351 of the PHS Act at the time of any approval. This would serve to protect the substantial investment in a product's development in the face of longer than expected FDA reviews, requests for Major Amendments, or multiple review cycles. In any of these instances, the application would remain eligible for approval. One exception could be a Refusal to File action, which is a finding that an application was not sufficiently complete to permit review. In that instance, no reviewable NDA would have been submitted before March 23, 2020 and only applications that are truly ripe for submission by March 23, 2020 would qualify. This proposed interpretation would recognize a narrowly tailored cohort of appropriately submitted applications for biological products under section 505 of the FD&C Act that could continue to be reviewed even once the listed drugs they reference are deemed to have a 351(a) license. This cohort of applications would eventually phase out as the applications are either approved or withdrawn.

This reading of the BPCI Act, which provides the ability to approve pending applications submitted under section 505 of the FD&C Act after March 23, 2020, and then deem them to be licenses, also aligns with FDA's interpretation of the applicability of the exclusivity provisions under the FD&C Act and PHS Act (i.e., in which only orphan drug exclusivity would apply to these approvals beginning March 23, 2020). *See* 2016 Draft Guidance at 6-7.

V. THERE IS FDA PRECEDENT FOR APPROVING APPLICATIONS THAT WOULD NOT QUALIFY FOR SUBMISSION AT THE TIME OF APPROVAL

In at least one other instance, FDA has determined that it can approve an application that was appropriately submitted under section 505 of the FD&C Act despite concerns that the application was no longer an acceptable submission at the time of approval. In 2002, L. Perrigo Company (Perrigo) submitted an application under section 505(b)(2) of the FD&C Act seeking approval of over-the-counter (OTC) loratadine. At the time of Perrigo's submission, Claritin (loratadine), the listed drug referenced in Perrigo's 505(b)(2) application, had only been approved as a prescription drug. Perrigo's product was otherwise identical to Claritin, but its application was submitted under 505(b)(2) rather than under 505(j) of the FD&C Act because the requested change to OTC status rendered the application ineligible for the 505(j) approval pathway. After the Perrigo application was filed and under FDA review, FDA approved a supplemental NDA (sNDA) to switch the listed drug, Claritin, from prescription to OTC status. Frommer, Lawrence, & Haug, LLP

then submitted a Citizen Petition asserting that Perrigo's section 505(b)(2) application was ineligible for approval because the OTC loratadine tablets described in the application were a duplicate of the listed drug, and thus could only be approved under section 505(j). In its June 24, 2004 Citizen Petition Response, FDA rejected this argument, stating "[a]fter an NDA, including one described by section 505(b)(2) of the [FD&C Act], has been appropriately submitted and is under review, FDA may refuse to approve the application only if one or more specific conditions warranting refusal apply.[1] These conditions are enumerated in the Act and the Agency's regulations.[2]" FDA, Response to Citizen Petition, Docket No. 03P-0160/CP1 & RC1, 4 (June 24, 2004). This principle, as articulated by FDA, is applicable when interpreting the "deemed to be a license" provision of the BPCI Act because the FD&C Act is clear in limiting the reasons for which FDA may refuse to approve a properly submitted and filed NDA. When applied, this principle clearly supports an interpretation of the "deemed to be a license" provision where applications are eligible for FDA review and approval after March 23, 2020 if they have been appropriately submitted under section 505 of the FD&C Act.

VI. FDA'S INTERPRETATION UNREASONABLY BURDENS SPONSORS OF 505(b)(2) APPLICATIONS AND IS CONTRARY TO THE PUBLIC HEALTH

The 2016 Draft Guidance creates an unreasonable burden on sponsors of biological products that have conducted their development program to support an application under section 505(b)(2) of the FD&C Act. Development programs for drugs and biological products take many years to advance and require millions of dollars of investment at each stage of development. At this point in time, less than four years from the 2020 transition date, many sponsors have already made these investments and will be in a position to submit an application under section 505(b)(2) of the FD&C Act prior to March 23, 2020. Prior to the issuance of the 2016 Draft Guidance, sponsors did not anticipate needing to obtain approval by March 23, 2020 and, as previously discussed, there is no way for sponsors to "evaluate whether a planned submission under section 505 of the FD&C Act would allow adequate time for approval of the NDA…" as FDA recommends. 2016 Draft Guidance at 7. Because these products are improvements to existing products, they would not be eligible for approval under section 351(k) of the PHS Act. The additional

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1 *See* 21 U.S.C. § 355(c)(1)(A) and 21 C.F.R. § 314.105(a).

2 *See* 21 U.S.C. § 355(d) and 21 C.F.R. § 314.125.

investment of time and money to repeat the studies that supported approval of the listed drug on which the proposed 505(b)(2) would have relied, in order to support approval under section 351(a) of the PHS Act, in most cases, is cost-prohibitive for sponsors as these improvements are not expected to generate similar revenue as the innovator product. While obtaining a right of reference from the application holder for the listed drug is an alternative option, there are anti-competitive incentives for the holders of those NDAs not to provide such a license. If these applications are no longer able to be reviewed and approved as 505(b)(2) NDAs after March 23, 2020, the time and money already invested may be wasted, and the patients that participated in clinical trials will have been put at unnecessary risk.

A simple example illustrates how almost any sponsor currently developing a biological product with the intent to submit an application under section 505(b)(2) of the FD&C Act could be unduly negatively affected by the 2016 Draft Guidance. A sponsor is currently enrolling a clinical study to support submission of an application for a biological product under section 505(b)(2) of the FD&C Act. The product is a change to a previously approved drug that is intended to improve patient care (e.g., change intravenous to oral route of administration to allow for self-administration rather than clinic visits, reformulate the drug so it could be taken once a day rather than three times a day). The projection of revenue from this innovation has generated investment dollars that have allowed the sponsor to conduct preclinical and Phase 1 clinical trials, as well as to conduct one future clinical trial that is anticipated to be needed to support approval. At the End-of-Phase 2 meeting, FDA agreed that the additional trial, if successful, will support a filing of the application. It is possible to receive the final readout of the clinical trial's results and compile an application for submission approximately two years from now (May 1, 2018). It is a positive trial and the application is filed by FDA, resulting in a PDUFA goal date for this standard review of February 1, 2019. On that date, the result of the first cycle review is a Complete Response Letter for a novel Chemistry, Manufacturing, and Controls (CMC) deficiency that was not previously anticipated by FDA or the sponsor. It will take eight months to resolve the CMC issue and resubmit the application (October 1, 2019). This Class 2 Resubmission has a new PDUFA goal date of April 1, 2020. FDA's review goes beyond March 23, 2020, thus never resulting in an action. The sponsor must withdraw the application and, based on its current development program and without repeating the studies already done by the reference product which the sponsor intended to rely on, has no approval pathway available under the PHS Act.

As this example hopefully illustrates, the uncertainty caused by the complex array of development and review issues that can arise, which could push potential approval beyond March 23, 2020, is the reality facing a number of sponsors today. FDA's interpretation,

despite providing a draft guidance four years prior to the end of the BPCI Act's transition period and implementation of the "deemed to be licensed" provision, is ineffective in permitting sponsors to plan their development programs.

VII. CONCLUSION

Not only does the FDA have flexibility in the interpretation of the "deemed to be a license" provision of the BPCI Act, but rules of statutory construction and the Agency's prior interpretations of the FD&C Act support a reading of this provision that would allow applications for biological products submitted under section 505 of the FD&C Act that are pending on March 23, 2020 to be reviewed and eligible for approval. Furthermore, we hope to have highlighted the likely negative impacts on sponsors and the public health that would be caused by FDA's proposed interpretation of the provision, which will impact a great number of ongoing development programs, causing irreparable financial harm to many sponsors, stifling innovation and availability of competition, and, putting countless patients at unnecessary risk.

Should you have any questions or desire clarifying information, please contact me at jtorrente@hpm.com or at (202) 737-7554.

Sincerely,

Josephine M. Torrente

JMT/JEV/cld