May 13, 2016

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

RE: Docket No. FDA-2015-D-4750
Draft Guidance for Industry, Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009

Dear Sir or Madam:

Novo Nordisk welcomes this opportunity to comment on the *Draft Guidance for Industry, Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009* ("Draft Guidance").

Novo Nordisk is a pioneer in biotechnology, a world leader in diabetes care and holds a leading position within hemostasis management, growth hormone therapy, and hormone therapy for women. Novo Nordisk manufactures and markets pharmaceutical products and services that make a significant difference to our patients, the medical profession, and society. More than 50% of our marketed and pipeline products are impacted by section 7002(e) of the Biologics Price Competition and Innovation Act of 2009 (BPCIA) and we appreciate FDA's attention to this matter.

FDA's Draft Guidance is important and very much appreciated. We also recognize the absence of direction to FDA from Congress on this provision of the BPCIA. This creates an increased challenge for FDA to interpret the BPCIA and provide transparent and legally sound guidance to industry that does not reach beyond FDA's authority. In the Draft Guidance, FDA proposes that any biological products approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA) would lose any periods of unexpired exclusivity, with the exception of orphan drug exclusivity, when these products are deemed licensed under section 351 of the Public Health Service Act (PHSA) on March 23, 2020. This includes any 5-year or 3-year data exclusivity, actual or potential pediatric exclusivity, and, potentially, 180-day exclusivity for section 505(j) applications. FDA's interpretation of the BPCIA, while likely well-intentioned, is very problematic and not consistent with Congress' intent to effectively transition a limited class of protein products from the FDCA to the PHSA, so that all protein products are treated uniformly in the long run. We respectfully request that FDA reconsider its positioning.

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1. FDA has interpreted the BPCIA such that exclusivity rights are inappropriately revoked from sponsors of approved drug products – an outcome clearly never intended by Congress

Since the passage of the BPCIA, Novo Nordisk has taken particular interest in the "transition" of products from New Drug Applications (NDA) to Biologics License Applications (BLA), especially given the impact of such a transition on our products that benefit patients with diabetes and growth hormone therapy related disorders. The BPCIA clearly provides a 10-year period during which sponsors can choose to submit either an NDA or BLA for certain classes of biological products that were already approved under section 505 of the FDCA.[1] Also under the BPCIA, this choice of pathway does not exist for follow-on applicants. Rather, follow-on sponsors need to submit an application under the same regulatory statute by which the reference product was "approved."[2] Congress intentionally gave this choice of application pathway to innovator/original sponsors so they could evaluate the regulatory and intellectual property aspects of their product and determine which pathway and package of intellectual property rights[3] was preferable. FDA's interpretation of the BPCIA ignores the choice of pathway provided in the language of the BPCIA by removing exclusivity rights granted under the pathway chosen by the sponsor – Such an outcome could not have been predicted by sponsors and was not intended by Congress based on the language of the statute.

The BPCIA emphasizes the terms "submitted" and "approved" throughout 7002(e)(1)-(3) because Congress intended for innovator/original product sponsors to have a choice of application pathway for filing purposes, statutory procedures and set of rights granted through approval for the chosen pathway. There is nothing in the BPCIA that implies the exclusivity rights granted under the chosen approval pathway should be revoked upon transition. From the time of enactment of the BPCIA on March 23, 2010, to the time of transition on March 23, 2020, a sponsor for an innovative/original product was given the opportunity to look at the approval pathways, the package of intellectual property and other rights granted upon approval, and the individual company circumstances for product development and application filings and then determine which pathway made the most sense for their individual product development program. If the sponsor chose the NDA pathway, then this is the pathway that the FDA would use to

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[1] Section 7002(e), An application for a biological product **may be submitted** under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) if—
(A) such biological product is in a product class for which a biological product in such product class is the subject of an application approved under such section 505 not later than the date of enactment of this Act; and
(B) such application—
(i) has been submitted to the Secretary of Health and Human Services (referred to in this subtitle as the "Secretary") before the date of enactment of this Act; or
(ii) is submitted to the Secretary not later than the date that is 10 years after the date of enactment of this Act.

[2] BPCIA, 7002(e)(3).

[3] The Agreement on Trade-Related Aspects of Intellectual Property Rights, Article 39.3, requires all World Trade Organization Members, when requiring as a condition of approving the marketing of pharmaceutical products which utilize new chemical entities, the submission of undisclosed test or other data, to protect that data against unfair commercial use. U.S. compliance with Article 39.3 for these required intellectual property protections is encompassed, in part, through the balance of exclusivity rights granted in the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act) and the BPCIA.

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evaluate the regulatory aspects of the application for approval. All rights conferred under that pathway should therefore follow the approval under the pathway which the sponsor chose. To interpret otherwise wreaks havoc on an otherwise fairly clear set of standards, rules and requirements outlined within each pathway. For example, it is very likely that ongoing FDCA litigation will be taking place on March 23, 2020. Congress could not have intended the courts to abandon a set of government standards, procedures and rights in the midst of litigation and have the courts apply a whole new set of standards, procedures and rights. However, FDA's current interpretation of the BPCIA would result in such an outcome.

In summary, Congress gave a 10-year period of application filing choice for innovator/original products and directed follow-on products to be filed under that same pathway. At the 10-year transition date, all applications must then be filed under section 351 of the PHSA. If the sponsor chose to file under the NDA pathway, then they should retain all their government granted intellectual property opportunities and rights under the Hatch-Waxman Act. This would include the 5-year data exclusivity right, the 3-year data exclusivity right, and the pediatric patent exclusivity right, as these are all part of the Hatch-Waxman Act package of rights available upon approval under the FDCA. The revocation of these rights is not consistent with the application filing options offered under the language of the BPCIA by Congress.

Furthermore, under section 7002(e)(4) of the BPCIA, Congress chose the language of the statute carefully. While the header of this section states "DEEMED APPROVED UNDER SECTION 351" the language Congress used for the application of the provision states "An approved application for a biological product under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) shall be deemed to be a license for the biological product under such section 351 on the date that is 10 years after the date of enactment of this Act." (emphasis added). The phrase "deemed to be a license" was purposely used in this provision specifically because Congress had to set a point in the future by which applications filed under section 505(b)(1) of the FDCA would be viewed for future filing purposes as licensed under section 351 of the PHSA. There had to be a set point in time where NDA applications transition over to BLA applications to serve as reference products for follow-on biosimilar filings under section 351(k) of the PHSA. Interpretation of the statute in this manner retains the government granted intellectual property rights under the approval pathway chosen by the sponsor, but creates a clear line of transition for future "filing" of all biological products under section 351 of the PHSA. It is also fully consistent with the plain meaning of "deemed" approved, as "deemed" means to "think of someone or something in a particular way."[4] Novo Nordisk strongly suggests that the BPCIA be interpreted such that the original approval pathway choice of the sponsor is respected and that the related exclusivities continue to apply in the same manner after transition.

2. FDA's removal of FDCA approved products from the Orange Book creates unnecessary confusion for effective understanding of product approval history and product transition to PHSA licensure for health care professionals and patients

[4] Miriam-Webster Dictionary, http://www.merriam-webster.com/dictionary/deem

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On page 6 of the Draft Guidance, FDA makes a sweeping statement that the "BPCIA does not explicitly provide a basis for the Agency to treat approved NDAs or ANDAs for biological products as both NDAs and BLAs after such applications are deemed to be BLAs on March 23, 2020."[5] For the reasons indicated above, we consider such an interpretation inappropriate based on the language of the statute, especially when considered in light of jurisprudence. Furthermore, removal of approved transition products from the Orange Book impairs the ability for an interested person to understand the pathway by which FDA approved a transition product, the process by which transition approved FDCA products moved to section 351(a) or 351(k) of the PHSA, and the historical nature of approval for any ongoing litigation based on the facts and circumstances at the time the case was filed.

FDA's decision to remove NDA products that transition to BLAs from the Orange Book is unnecessary and does not address the need to provide transparent and historically appropriate approval information to the public at large. Nothing in the statute indicates that a transition product that was approved under an NDA loses that approval under the language of the BPCIA, and nothing in the statute indicates it should. The language of the statute does not require removal from the Orange Book as the FDCA is the pathway by which the product was approved. However, FDA could and should make a notation in the Orange Book to identify products that transitioned from NDA to BLA. This is critically important for follow-on product development and filing purposes

Furthermore, withdrawal from the Orange Book could, inappropriately, be interpreted by health care practitioners (HCPs) as a statement by FDA that the biological product is no longer an approved product. This is especially true since removal from the Orange Book often occurs when a product has been withdrawn. It is noteworthy that FDA makes reference in its Draft Guidance that these products will be removed from the Orange Book[6], but does not make any determination as to if or how transition products will be listed in the Purple Book. Upon the transition date, FDA should list transition products immediately in the Purple Book, otherwise they will essentially be left homeless and without any status in regard to their ability to serve as reference products or as biosimilars or interchangeable products. Retention of products approved under the FDCA in the Orange Book, permits follow-on sponsors to identify which pathway was used for reference product approval and permits a smooth transition of biological products from the FDCA pathway to the PHSA pathway over time.

Documentation in the Purple Book or Orange Book that transition products are licensed is necessary, especially for those products that are manufactured outside of the US at the time of transition. US Customs may delay release of the product at the border if neither the sponsor nor the relevant FDA databases have the information to demonstrate that the product is licensed and allowed for interstate commerce. This could create unnecessary drug shortages and related

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[5] Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009, Draft Guidance for Industry, March 2016, Procedural, lines 171 to 173.
[6] Id. at 6, lines 173-175.

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hardships for patients. Furthermore, lack of documentation of licensure may result in confusion by both HCPs and patients that the prescribed product was withdrawn by FDA or lacks status as an approved or licensed therapy. This situation would not be in the best interest of patients, caregivers, HCPs, sponsors, or FDA.

It is important to effectively, efficiently, and transparently transition these products from the NDA pathway to the BLA pathway, recognizing that Congress was attempting to streamline the process and not harm sponsors or patients, or confuse HCPs in the process. Thus, FDA should respect the historical peculiarities of these transition products and ensure that the government granted intellectual property rights remain in force, by leaving these products in the Orange Book, making a notation within the Orange Book that these products are deemed licensed as section 351(a) or 351(k) products, as appropriate, as of March 23, 2020, and then listing the products in the Purple Book with their appropriate status with a licensure date of March 23, 2020.

3. FDA should consider the Takings Clause of the Fifth Amendment of the U.S. Constitution and precedential jurisprudence when interpreting section 7002(e) of the BPCIA

The Takings Clause of the Fifth Amendment of the United States Constitution ("Takings Clause") provides that private property shall not be taken without just compensation.[7] Additionally, the U.S. Supreme Court has clarified through several decisions, one decided as recently as 2015, that intellectual property is personal property and is protected by the Takings Clause of the Fifth Amendment.[8] As quoted by Chief Justice Roberts in Horne v. U.S. Department of Agriculture, "The Government has broad powers, but the means it uses to achieve its ends must be 'consist[ent] with the letter and spirit of the constitution.' McCulloch v. Maryland, 4 Wheat. 316, 421 (1819)." In extinguishing exclusivity rights granted under the NDA pathway upon transition to the BLA pathway, FDA has interpreted the BPCIA in a way that entirely "takes" the intellectual property rights of the owner and provides no just compensation for this taking. Thus, FDA's interpretation of the BPCIA is flawed and not consistent with Congress' intent, as Congress could not have intended to pass legislation inconsistent with the U.S. Constitution.

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[7] Fifth Amendment of the United States Constitution, "No person shall be held to answer for a capital, or otherwise infamous crime, unless on a presentment or indictment of a Grand Jury… nor be deprived of life, liberty, or property, without due process of law; **nor shall private property be taken for public use, without just compensation**." (emphasis added).

[8] Horne et al. v. Department of Agriculture 576 U.S._ (2015), held that the Takings Clause imposes a "categorical duty" on the government to pay just compensation whether it takes personal or real property. James v. Campbell, 104 U.S. 356, 358 (1882), a case concerning the alleged appropriation of a patent by the Government: "[A patent] confers upon the patentee an exclusive property in the patented invention which cannot be appropriated or used by the government itself, without just compensation, any more than it can appropriate or use without compensation land which has been patented to a private purchaser." Ruckelshaus v. Monsanto,104 U.S. 2862 (1984) where the United States Supreme Court held that just compensation is required under the taking clause of the fifth amendment when the government appropriates health and safety data after having explicitly assured the submitter at the time of submission that the data would not be used for any purpose other than those specifically mentioned in the regulation.

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In the Draft Guidance, FDA categorically states, "Moreover, with the exception of orphan drug exclusivity, the exclusivity provisions of the FD&C Act serve to limit the submission or approval of applications under section 505 of the FD&C Act, but not under section 351 of the PHS Act… Accordingly, any unexpired period of exclusivity associated with an approved NDA for a biological product subject to section 7002(e) of the BPCI Act (e.g., 5-year exclusivity, 3-year exclusivity, or pediatric exclusivity) would cease to have any effect, and any patents listed in the Orange Book would no longer be relevant for purposes of determining the timing of approval of a 505(b)(2) application (or ANDA)."[9] Furthermore, FDA fails to provide any interpretation of the BPCIA that compensates for the removal of FDCA granted intellectual property rights upon transition to the PHSA. As discussed above, Supreme Court precedent supports that removal of these granted Hatch-Waxman intellectual property rights from the sponsor without providing any just compensation is a taking of private property rights by the government. Such an interpretation not only ignores the BPCIA "choice of filing," but introduces a legal and judicial outcome that raises Constitutional issues. This is especially true given that other interpretations would avoid serious Constitutional questions.

Conflict with the Takings Clause could be avoided by interpreting the language of the BPCIA so that the intellectual property rights granted to the sponsor under the FDCA (5-year or 3-year data exclusivity, 180 day ANDA exclusivity (if applicable), and pediatric exclusivity), based on the sponsor's choice of pathway, continue to apply after transition until they naturally expire. Such an interpretation of section 7002(e) of the BPCIA not only prevents conflict with the Takings Clause, but also avoids upsetting and creating greater uncertainty around any ongoing court litigation between sponsors. Furthermore, retaining transition products in the Orange Book maintains the necessary historical understanding of which products were filed under the FDCA prior to the transition period. Hatch-Waxman intellectual property rights are issued for a limited duration of time, permitting these rights to naturally expire and move toward full transition of protein products into the PHSA pathway over time as Congress intended. Finally, if FDA makes clear in guidance that the procedural process for handling intellectual property rights is controlled through the pathway by which the reference product was filed, there is no uncertainty or unfair application of intellectual property rights while the transition progresses. We urge FDA to reconsider its interpretation of section 7002(e) of the BPCIA with regard to product exclusivity, because we strongly believe Congress did not intend to pass legislation inconsistent with rights granted under the U.S. Constitution.

4. **Several key regulatory questions resulting from differences in the FDCA and PHSA and related regulations remain and are in need of clarification.**

While the Draft Guidance provides clarity in some areas, several issues remain that have not yet been addressed. Novo Nordisk requests FDA expeditiously provide further guidance and clarity on the following:

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[9] Draft Guidance, lines 182-192.

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Page No.	Line No.	Comment
General		How is a sponsor supposed to handle updates (e.g. manufacturing, safety, efficacy updates, etc.) to an NDA approved transition product just prior to the March 23, 2020, transition date? Can a sponsor file as a BLA referencing the NDA if they believe the FDA review may extend beyond the March 23, 2020 date?
General		Under 21 CFR 601.2, manufacturers are required to submit samples, but a similar requirement does not exist under 21 CFR 211. Will samples be required for transition products after the transition date for approved NDA products even though they were not required prior to this date? Will FDA waive this requirement for transition products?
General		FDA should make clear that, after the transition, licensed transition products will remain within the same review office in the same division as the currently approved NDA product.
General		FDA should make clear that, after the transition, transition products will remain within the same inspection program as prior to transition.
General		FDA should clarify how to handle reference to previously approved FDCA transition products, especially with respect to combination products where the combination product is made up of polypeptide sequences where one component remains under the NDA pathway and the other component transitions to the BLA pathway. We suggest that under this circumstance the BLA for the combination product should be able to cross reference to relevant parts of previously approved NDA drug component under FDCA.
General		FDA should publish a full list of approved NDA products that will transition to BLA products and specify whether those products will be designated reference products or not under 351(a).
General		FDA needs to clarify their handling of transition products that are fixed-combination drugs that will become combination products, where one constituent part remains in the FDCA pathway and the other constituent part transitions to the BLA pathway. FDA's combination product regulations define primary mode of action as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product." (emphasis added) 21 CFR 3.2(m). FDA must address which constituent party they believe has the "single primary mode of action" or at least indicate how they plan to work with the sponsor to determine such criteria, since this determination will affect whether the product transitions or not.

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6	197-199	FDA has not provided any guidance on how post-approval commitments and requirements (PMRs/PMCs) should be handled if they occur around March 23, 2020. Compliance dates were set at time of approval based on the time necessary to compile such data. Would delaying the submission to avoid review on March 23, 2020, be a sufficient justification to change the compliance dates?
5	Footnote 7	Under the NDA pathway there is no manufacturing license issued by FDA. But, under the BLA pathway, a manufacturing license is required under Section 351(a) of the PHSA in order to market in interstate commerce. FN 7 indicates that FDA will address BLA numbers at a later time. Will FDA be replacing NDA numbers with BLA numbers? Or is FDA issuing a different BLA manufacturing license and/or letter of approval given that this Draft Guidance does not seem to grant NDA transition products a date of first licensure? We request FDA expeditiously address these questions for planning purposes.
7	Footnote 12	In footnote 12, FDA mentions considerations with respect to Type 2 DMFs. What about other DMF types? Ideally, if the application has been referencing other DMF types (II, IV or V) prior to transitioning, the application should be able to continue referencing the DMF. Is this the case?

Thank you for the opportunity to provide comments on this guidance. We ask FDA to reconsider their interpretation of section 7002(e) of the BPCIA and expeditiously issue new guidance. We would be pleased to provide further input or clarification of our comments if needed.

Sincerely,

Richelle Tompa on behalf of RBC

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