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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: Implementation of the "Deemed To Be a License" Provision of the Biologics Price Competition and Innovation Act of 2009; Draft Guidance for Industry, 81 Fed. Reg. 13373 (Mar. 14, 2016)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to provide comments on the Food and Drug Administration's (FDA's) draft guidance for industry entitled "Implementation of the 'Deemed to be a License' Provision of the Biologics Price Competition and Innovation Act of 2009" (Draft Guidance). PhRMA represents the country's leading innovative biopharmaceutical research companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier and more productive lives. Since 2000, PhRMA member companies have invested more than half a trillion dollars in the search for new treatments and cures, including an estimated $58.8 billion in 2015 alone.

PhRMA commends FDA for releasing draft guidance on the agency's approach to the implementation of the "transition provisions" of the Biologics Price Competition and Innovation Act of 2009 (BPCIA) located in section 7002(e) of the Affordable Care Act and, in particular, section 7002(e)(4). This provision states that "[a]n approved application for a biological product under section 505 of the Federal Food, Drug, and Cosmetic Act [(FDCA)] shall be deemed to be a license for the biological product under such section 351 [of the Public Health Service Act (PHSA)] on the date that is 10 years after the date of enactment of [the BPCIA]," i.e., March 23, 2020.[1] PhRMA supported the enactment of the BPCIA and has actively participated in FDA's ongoing efforts to implement the statute.

I. Executive Summary

PhRMA has serious concerns with the Draft Guidance, because, among other things we believe that the agency is misinterpreting the BPCIA in a manner that would harm the incentives of sponsors to innovate and bring new treatments to patients. We strongly recommend that FDA reconsider its proposed interpretation of the transition provisions and substantially revise the Draft Guidance. FDA should do so on an expedited basis and well in advance of March 23, 2020, because clear and timely guidance is critical for sponsors of

[1] Pub. L. No 111-148, Title VII, Subtitle A, § 7002(e)(4), 124 Stat. 119, 817 (2010) (citation omitted).

biological products that fall within a product class subject to the transition provisions (referred to herein as transition biological products). PhRMA's concerns with the Draft Guidance are outlined below.

First, the Draft Guidance's interpretation of statutory regulatory exclusivity requirements—and particularly, FDA's proposal to extinguish unexpired Hatch-Waxman and pediatric exclusivity for transitioning new drug applications (NDAs) and also to deny these applications any reference product exclusivity under section 351(k)(7) of the PHSA—is inconsistent with the BPCIA and would significantly harm incentives for medical innovation.[2] For transition biological products, FDA could have interpreted the "first licensure" date from which reference product exclusivity runs under section 351(k)(7) to be any of the following: (1) the date on which the NDA is deemed to be a biologics license application (BLA); (2) the date on which FDA approved the NDA for the transition biological product; or (3) the date that provides reference product exclusivity that would expire on the date that Hatch-Waxman exclusivity would have expired. FDA also could have determined that the NDA exclusivity framework would continue to apply to transition biological products for a period of time after March 23, 2020, given the flexibility inherent in Congress's use of the word "deemed." Instead, the agency proposes that the "first licensure" provision would not apply to transition biological products with approved NDAs.[3]

The agency's reading is by far the least natural reading of the BPCIA. It is inconsistent with other parts of the Draft Guidance and statutory provisions. The Draft Guidance also raises constitutional issues concerning a taking of private property without just compensation in violation of the Fifth Amendment and threatens the nation's compliance with its free trade agreements. PhRMA believes the most natural reading of the BPCIA is that the first licensure occurs on the date on which a transition biological product is deemed licensed under the PHSA. We understand FDA has concerns with this literal reading of the statute and therefore urge FDA to embrace a compromise approach—one that harmonizes the BPCIA with the FDCA.

Specifically, given the flexibility conferred by Congress's use of the word "deemed" in section 7002(e)(4), FDA should interpret the intellectual property provisions of the Hatch-Waxman Act to continue to apply to transition biological products until the last *Orange Book*-

[2] Draft Guidance, lines 190–91 (proposing that any unexpired period of Hatch-Waxman or pediatric exclusivity earned by the applicant under the FDCA "would cease to have any effect"); *id.*, lines 201–06 (proposing that NDAs for biological products that are deemed to be BLAs will receive no reference product exclusivity). FDA proposes that transition biological products will retain their orphan exclusivity "because orphan drug exclusivity can be granted to and can block the approval of a drug approved under section 505 of the [FDCA] or a biological product licensed under section 351 of the [PHSA]." *Id.*, lines 192–97.

[3] *Id.*, lines 214–18 ("FDA interprets section 7002(e) of the [BPCIA] together with section 351(k)(7) of the [PHSA] such that the phrase 'the date on which the reference product was first licensed under subsection (a)' in section 351(k)(7)(A) and (B) of the [PHSA] does not apply to biological products that will be deemed to have a license under section 351(a) of the [PHSA] on March 23, 2020.").

listed patent for a listed drug has expired. This interpretation would create the fewest inequities and the least disruption: already-granted exclusivity would remain in place and would not be shortened or lengthened, all follow-on applicants would be treated equally, and ongoing Hatch-Waxman patent litigation could continue without interruption. This interpretation also is most consistent with section 7002(e)(2) of the BPCIA, which allows sponsors of innovative transition biological products to choose between the NDA and BLA pathways—and their attendant packages of rights—until March 23, 2020. We urge FDA to revise the Draft Guidance to adopt this reading and avoid the above issues.

Second, FDA's proposal that NDAs pending on March 23, 2020—including NDAs that have been tentatively approved—would not be finally approved and would need to be withdrawn and resubmitted under the PHSA is contrary to the plain language of the BPCIA. The statute preserves sponsors' ability to submit applications under section 505 of the FDCA until March 23, 2020. FDA's proposed interpretation also is unduly burdensome and would unnecessarily delay patient access to new medical treatments. FDA's proposal would create a blackout period during which applicants would be unable to submit either NDAs or BLAs for their proposed medicines. For instance, the sponsor of a follow-on transition biological product would be unable to submit a biosimilar application (due to the lack of a reference product, the originator application having not yet been "deemed licensed") *and* unable to submit a section 505(b)(2) application (because there is insufficient time to secure approval). Similarly, because FDA's proposed approach seemingly would apply to pending supplemental NDAs, it could hamper efforts by sponsors to introduce product improvements and ensure consistent drug supply in the lead up to March 23, 2020. PhRMA believes that FDA should instead provide that NDAs and supplemental NDAs that are pending on March 23, 2020 will retain their status until approval, at which time they would be deemed to be BLAs or supplemental BLAs, respectively, for purposes other than intellectual property rights. This approach would be far less disruptive and would ensure that new substantive requirements are not imposed on pending applications.

Finally, the Draft Guidance leaves unanswered critical questions about implementation of the transition provisions, including whether applications under section 505 of the FDCA will be deemed licensed under section 351(a) or section 351(k) of the PHSA, whether FDA intends to list transition biological products in the *Purple Book*, how FDA proposes to treat transition biological products for which there was a determination of therapeutic equivalence in the *Orange Book*, what technical application rules (e.g., cGMP, postmarketing reporting, and supplement requirements) will apply to transition biological products, and what nonproprietary naming convention will apply to transition biological products, among other issues. It is imperative that FDA address these issues promptly, as less than half of the transition period remains and affected sponsors need to plan accordingly.

II. FDA Should Take a Very Different Approach to its Proposal Regarding Exclusivity in the Context of Transition Biological Products

FDA's proposal effectively to terminate any remaining FDCA exclusivity for approved transition biological products would harm incentives that were carefully crafted by Congress to incentivize medical innovation. The Draft Guidance on these points is internally inconsistent and conflicts with plain statutory language. Also, the Draft Guidance raises significant constitutional and international trade issues. PhRMA's proposed alternative interpretation avoids these concerns and strikes a balance between the public policy needs to recognize exclusivity earned by sponsors of transition biological products and facilitate timely approval of follow-on products.

A. *The Draft Guidance content on exclusivity is internally inconsistent.*

FDA's proposal to eliminate FDCA exclusivity for transition biological products while also denying them PHSA exclusivity is unsound, as the agency relies selectively and inconsistently on literal readings of FDCA and PHSA provisions and purported Congressional intent.

While FDA states that it strictly construes the statutory provisions to propose extinguishing FDCA exclusivity, it simultaneously ignores the plain language of the PHSA in its proposal to deny transitioning NDAs reference product exclusivity. In proposing that FDCA exclusivities "would cease to have any effect"[4] on the transition date, the agency emphasizes that "the exclusivity provisions of the [FDCA] serve to limit the submission or approval of applications under section 505 of the [FDCA], but not under section 351 of the PHS Act," and that the BPCIA provides that "no applications for biological products may be submitted under section 505 of the [FDCA] after March 23, 2020."[5] In contrast, FDA disregards the plain language of section 351(k)(7) of the PHSA in concluding that transition biological product applications will receive no reference product exclusivity. Under the PHSA, reference product exclusivity runs from "the date on which the reference product was first licensed under subsection (a)."[6] There is nothing in this language that prohibits application of reference product exclusivity to applications originally submitted as NDAs. Quite literally, products that were previously approved under NDAs will be first licensed under the PHSA when the NDAs are deemed BLAs on March 23, 2020. Moreover, they will not meet the statutory definition of "reference product"[7] until that day—a fact FDA implicitly recognizes elsewhere in the Draft

[4] *Id.*, lines 188, 190–91.

[5] *Id.*, lines 184–86.

[6] PHSA § 351(k)(7)(A) & (B).

[7] *Id.* § 351(i)(4) ("The term 'reference product' means the single biological product *licensed under subsection (a)* against which a biological product is evaluated in an application submitted under subsection (k).") (emphasis added).

Guidance.[8] Therefore, the best literal reading of the BPCIA is that a transition biological product with an approved NDA is "first licensed" on March 23, 2020.

Nevertheless, FDA proposes to read the phrase "the date on which the reference product was first licensed under subsection (a)" out of the statute for transitioning NDAs.[9] In other words, FDA regards transition biological products with approved NDAs as having no first licensure date, in conflict with the plain language of the statute. The agency relies upon assumptions about Congressional intent to support its proposed interpretation:

> [n]othing in the [BPCIA] suggests that Congress intended to grant biological products approved under section 505 of the [FDCA] . . . a period of exclusivity upon being deemed to have a license under the [PHSA] that would impede biosimilar or interchangeable product competition in several product classes until the year 2032.[10]

FDA does not point to any evidence of this supposed Congressional intent. But in any case, the agency's approach to interpreting the first licensure provision contrasts sharply with the agency's approach to interpreting the FDCA exclusivity provisions. Whereas FDA relies upon assumptions about Congressional intent, rather than the language of the statute, in denying reference product exclusivity to transition biological products, the agency does not discuss Congressional intent in describing its highly technical reading of the Hatch-Waxman and pediatric exclusivity provisions.

Other passages of the Draft Guidance reflect similar inconsistencies in approach. For example, the agency acknowledges that the BPCIA "is silent regarding implementation"[11] of the transition provisions, presumably implying that FDA has discretion to implement the statute in any appropriate manner. In contrast, in another passage, the Draft Guidance says that the statute "does not explicitly provide a basis" for FDA to treat applications approved under

[8] *See, e.g.*, Draft Guidance, lines 269–72 (explaining that the development program for a section 505(b)(2) application under the FDCA could be modified to "support submission of a 351(k) BLA for a proposed biosimilar product or a proposed interchangeable product *at such time as there is a biological product licensed under section 351(a) of the [PHSA] that could be a reference product*") (emphasis added); *id.*, lines 290–94 ("A sponsor of a proposed biological product that could meet the requirements for a proposed biosimilar and other applicable requirements would be able to submit a 351(k) BLA that cites the listed drug as its reference product after the NDA for the listed drug is deemed to be a BLA (or after another product that could be a reference product for the proposed product is licensed under section 351(a) of the [PHSA]).").

[9] *See supra* note 3.

[10] Draft Guidance, lines 210–14.

[11] *Id.*, lines 137–38.

section 505 of the FDCA as both NDAs and BLAs after the transition date.[12] In this case, FDA apparently interprets silence as constraining its authority.

B. *The Draft Guidance's exclusivity content is in tension with the statutory language.*

FDA's proposal to provide no exclusivity for transition biological product NDAs conflicts with express statutory terms in at least four respects.

First, the Draft Guidance is in tension with section 7002(e)(2) of the BPCIA. Under this provision, applicants "may" continue to submit NDAs for transition biological products if the NDAs are "submitted . . . *not later than* the date that is 10 years after the date of enactment of this Act," among other things.[13] In other words, by legislative design, sponsors of innovative transition biological products have a choice of the NDA or BLA approval pathways up to and until March 23, 2020. If Congress meant to burden this choice and restrict the exclusivity of applicants who chose the NDA pathway during this transition, surely it would have been more explicit.[14] Instead, the better reading is that Congress intended the NDA pathway—with all attendant rights, including exclusivity—to remain available at the sponsors' discretion. FDA's proposed approach does not fully credit the sponsor's choice to pursue the NDA approval pathway as contemplated by Congress.

Second, the Draft Guidance over-reads the word "deemed." When courts have been confronted with the word "deem" in the absence of a statutory definition—as is the case with the BPCIA—they turn to the term's ordinary meaning.[15] According to Black's Law Dictionary, "deem" means "[t]o treat (something) as if (1) it were really something else, or (2) it had qualities that it does not have."[16] In other words, it creates a legal fiction, and the thing exists as something else only as a matter of law, not as a matter of fact. This distinction means that there can be limits to the degree with which the "deemed" thing is treated as the same as the actual thing.[17] Put simply, "deemed" does not have to mean "is." A comparison with antibiotic

[12] *Id.*, lines 171–73.

[13] Pub. L. No 111-148, Title VII, Subtitle A, § 7002(e)(2), 124 Stat. 119, 817 (2010) (emphasis added).

[14] *See FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 160 (U.S. 2000) (explaining that Congress would not legislate an economically and politically significant issue in a "cryptic" fashion).

[15] *See, e.g.*, *Martin v. Shinseki*, 26 Vet. App. 451, 457 (Vet. App. 2014); *Puerto Rico Tel. Co. v. SprintCom, Inc.*, 662 F.3d 74, 95 (1st Cir. 2011) (explaining "deem" is a word "of common legal usage").

[16] BLACK'S LAW DICTIONARY 504 (10th ed. 2014) ("'Deem' has been traditionally considered to be a useful word when it is necessary to establish a legal fiction either positively by 'deeming' something to be what it is not or negatively by 'deeming' something not to be what it is." (quoting G.C. Thornton, Legislative Drafting 99 (4th ed. 1996))).

[17] *See Lin v. Bureau of Citizenship & Immigration Servs.*, 514 F.3d 251, 255 (2d Cir. 2008) (finding reasonable Board of Immigration Appeals' decision that even if plaintiff "was considered 'deemed' to have had a visa petition approved for purposes of [adjusting his status to that of legal permanent resident under the Chinese Student (continued…)

transition provisions in the Food and Drug Administration Modernization Act of 1997 (FDAMA) illustrates how FDA has some flexibility in reading "deemed" in section 7002(e)(4) as long as its approach is consistent with other applicable statutory provisions. In FDAMA, Congress provided that an antibiotic drug application approved under section 507 of the FDCA on the day before FDAMA's enactment:

> shall, on and after such date of enactment, be considered to be an application that was submitted and filed under section 505(b) of [the FDCA] and approved for safety and effectiveness under section 505(c) of [the FDCA], except that if such application for marketing was in the form of an abbreviated application, the application shall be considered to have been filed and approved under section 505(j) of [the FDCA].[18]

The BPCIA's transition provisions do not state that a transitioning NDA will "be considered to be an application that was submitted and filed under" the PHSA or that the product will be considered licensed for safety, purity, and potency under the PHSA. Rather, the BPCIA's transition language is less rigid, thus giving the agency a certain degree of leeway to develop a workable and fair implementation approach that is consistent with other statutory provisions. In this regard, FDA's conclusion that the statute "does not explicitly provide a basis" for FDA to treat applications approved under section 505 of the FDCA as both NDAs and BLAs after the transition date misses the mark.[19] Congress's use of the word "deemed" provides the agency with flexibility to take this approach.

Third, the Draft Guidance ignores that Congress has already explicitly addressed which applications do not qualify for reference product exclusivity; as such, FDA's addition of biological products with deemed BLAs to this explicit statutory list oversteps the agency's authority. FDA itself has explained that a section 351(a) application "may be eligible for a period of exclusivity that commences on the date of its licensure *unless its date of licensure is not considered a date of first licensure* ***because it falls within an exclusion under 351(k)(7)(C) [of the PHSA]***."[20] Two such exclusions are listed under section 351(k)(7)(C):

Protection Act], he did not, in fact, 'file' an approvable visa petition under § 204(a) [of the Immigration and Nationality Act (INA)] as required by INA § 245(i), and was therefore not eligible to adjust under that provision.") (citations omitted).

[18] FDAMA, Pub. L. No. 105-115, § 125(d)(1), 111 Stat. 2296, 2326–27 (1997).

[19] Draft Guidance, lines 171–73.

[20] FDA, Draft Guidance for Industry, Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act, lines 96–98 (Aug. 2014) (emphases added).

- the date of licensure of "a supplement for the biological product that is the reference product;"[21] and

- the date of licensure of "a subsequent application filed by the same sponsor or manufacturer of the biological product that is the reference product (or a licensor, predecessor in interest, or other related entity) for—(I) a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or (II) a modification to the structure of the biological product that does not result in a change in safety, purity, or potency."[22]

Congress was well aware that transition biological product NDAs could be deemed applications under section 351(a) of the PHSA come March 23, 2020; the "deemed to be a license" provision was enacted simultaneously with section 351(k)(7). The fact that Congress enumerated the above applications ineligible for reference product exclusivity and did not include deemed BLAs in the list indicates that Congress did not intend to exclude these deemed BLAs from reference product exclusivity.[23] This conclusion is consistent with the principle that, where Congress has expressly provided exceptions in a statute, others should not be implied.[24] Thus, as noted above, the best literal reading of the statute is that transition biological products with approved NDAs will be "first licensed" on March 23, 2020.

Finally, the Draft Guidance's proposal that pediatric exclusivity for transition biological product applications would "cease to have effect" on March 23, 2020 conflicts with the intent behind section 351(m) of the PHSA. In this provision—which also was enacted concurrently with the transition provisions—Congress expressly provided pediatric exclusivity for BLAs. Although pediatric exclusivity under the PHSA attaches to some different exclusivity periods than under the FDCA,[25] Congress's intent is clear: pediatric exclusivity is available to BLA

[21] PHSA § 351(k)(7)(C)(i).

[22] *Id.* § 351(k)(7)(C)(ii)(I)–(II).

[23] *See Leatherman v. Tarrant County Narcotics Intelligence & Coordination Unit*, 507 U.S. 163, 168 (1993) (discussing the "*expressio unius est exclusio alterius*" canon of statutory construction); *cf. Lindh v. Murphy*, 521 U.S. 320, 330 (1997) ("[N]egative implications raised by disparate provisions are strongest when the portions of a statute treated differently . . . were being considered simultaneously when the language raising the implication was inserted.").

[24] *See, e.g.*, *United States v. Johnson*, 529 U.S. 53, 58 (2000) ("When Congress provides exceptions in a statute, it does not follow that courts have authority to create others. The proper inference . . . is that Congress considered the issue of exceptions and, in the end, limited the statute to the ones set forth."); *Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 395 (5th Cir. 2008) (concluding that compounded drugs are not exempt from the definition of "new drug" under the FDCA, reasoning that the statute carves out specific exceptions and compounded drugs are not among them).

[25] *Compare* PHSA § 351(m)(2) & (m)(3) *with* FDCA § 505A(b)(1) & (c)(1).

sponsors on the same terms as to NDA sponsors under section 505A of the FDCA. Section 351(m)(1) states that the provisions of section 505A on issuance and fulfillment of written requests "shall apply with respect to the extension of a period" for BLAs "to the same extent and in the same manner as such provisions apply with respect to the extension of a period under [section 505A]." Moreover, Congress used nearly identical language to describe eligibility for pediatric exclusivity for NDAs and BLAs.[26] Under FDA's proposed interpretation, a sponsor could have received a written request and invested significantly in pediatric trials to satisfy that request, in accordance with the terms of both the PHSA and FDCA, only to lose that exclusivity completely upon the transition. The agency's proposal would have the perverse result of stripping transition biological products awarded both orphan drug exclusivity and pediatric exclusivity of the latter, even though both the FDCA and the PHSA provide that pediatric exclusivity will extend orphan drug exclusivity.[27]

C. *The Draft Guidance's content raises serious constitutional questions concerning improper takings in violation of the Fifth Amendment.*

FDA's proposal to extinguish unexpired exclusivity rights presents serious constitutional problems. Under the canon of constitutional avoidance, the BPCIA can—and therefore must—be read to avoid the significant Takings Clause issues raised by the agency's proposal.[28]

The Fifth Amendment to the U.S. Constitution forbids the government from taking private property without just compensation.[29] Holders of NDAs with unexpired periods of Hatch-Waxman and pediatric exclusivity have two distinct but related property rights that are protected by the Takings Clause. First, application holders have a property right in their trade

[26] *Compare, e.g.*, PHSA § 351(m)(3) ("If the Secretary determines that information relating to the use of a licensed biological product in the pediatric population may produce health benefits in that population and makes a written request to the holder of an approved application under subsection (a) for pediatric studies (which shall include a timeframe for completing such studies), the holder agrees to the request, such studies are completed using appropriate formulations for each age group for which the study is requested within any such timeframe, and the reports thereof are submitted and accepted in accordance with section 505A(d)(3) of the [FDCA]," pediatric exclusivity shall apply) *with* FDCA § 505A(c)(1) ("[I]f the Secretary determines that information relating to the use of an approved drug in the pediatric population may produce health benefits in that population and makes a written request to the holder of an approved application under section 505(b)(1) for pediatric studies (which shall include a timeframe for completing such studies), the holder agrees to the request, such studies are completed using appropriate formulations for each age group for which the study is requested within any such timeframe, and the reports thereof are submitted and accepted in accordance with subsection (d)(3)," pediatric exclusivity shall apply).

[27] *See* FDCA § 505A(b)(1)(A)(ii) & (c)(1)(A)(ii); PHSA § 351(m)(2)(B) & (m)(3)(B).

[28] *See Nat'l Mining Ass'n v. Kempthorne*, 512 F.3d 702, 711-12 (D.C. Cir. 2008) (canon of constitutional avoidance applies to Takings Clause where an "an agency interpretation . . . create[s] an 'identifiable class' of takings victims").

[29] U.S. CONST. amend. V.

secrets,[30] which they developed at considerable expense and disclosed to FDA based on an explicit statutory promise of exclusivity. Second, application holders have a property right in regulatory exclusivity itself. FDA's proposed implementation of the BPCIA would effect a taking of these property rights.

In *Ruckelshaus v. Monsanto*, the Supreme Court held that Monsanto had a property right in trade secrets—health, safety, and environmental data—that it submitted to the Environmental Protection Agency in order to obtain a pesticide registration.[31] The Court explained that "[t]he economic value of that property right lies in the competitive advantage over others that Monsanto enjoys by virtue of its exclusive access to the data."[32] It further held that companies that submitted health, safety, and environmental data to the EPA between 1972 and 1978 had a "reasonable investment-backed expectation" that their trade secrets would not be used or disclosed without authorization.[33] During that period, anyone submitting data to the EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) was able to "protect its trade secrets from disclosure."[34] Under the statute, Monsanto had "explicit assurance that EPA was prohibited from disclosing publicly, or considering in connection with the application of another," its data.[35] Accordingly, the EPA's "consideration" of Monsanto's trade secrets submitted pursuant to FIFRA in review of a competitive application during that period constituted a taking.[36]

Pharmaceutical companies have comparable property rights in the trade secrets they develop and submit to FDA to establish the safety and efficacy of their products and to assess safety and effectiveness issues in pediatric populations. Under the Hatch-Waxman and pediatric exclusivity provisions, applicants submit their valuable trade secrets with a similarly "explicit assurance" that FDA will not accept or approve (as appropriate) competitive applications that rely directly or indirectly on those trade secrets until applicable statutory

[30] Here, we refer to trade secrets as recognized under state law. *See Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1001 (1984) (discussing Missouri state law, which recognizes trade secrets as defined in the Restatement of Torts as property, and holding that such trade-secret property right is protected by the Takings Clause). The Restatement of Torts definition of "trade secret" used in that case encompassed "any formula, pattern, device or compilation of information which is used in one's business, and which gives him an opportunity to obtain an advantage over competitors who do not know or use it." RESTATEMENT (FIRST) OF TORTS § 757 cmt. b (1939).

[31] 467 U.S. 986 (1984).

[32] *Id.* at 1012.

[33] *Id.* at 1010–12.

[34] *Id.* at 1010.

[35] *Id.* at 1011.

[36] *Id.* at 1012.

periods of exclusivity expire.[37] As in *Monsanto*, acceptance or approval of a competitor's application prior to the expiration of exclusivity as it was originally promised would constitute a taking.

In addition to trade secrets, applicants have related property rights in statutory exclusivity itself. As courts have observed in recognizing patents as property for purposes of the Takings Clause, "the right to exclude . . . is but the essence of the concept of property."[38] Like a patent, exclusivity is a valuable intellectual property right that excludes others from submitting or obtaining approval of an application for a competitive product for a period of time.[39] For this reason as well, FDA may not rescind an unexpired period of exclusivity without just compensation.

The BPCIA does not purport to require the termination of exclusivity or dictate that the agency allows the use of an NDA holder's trade secrets prior to the expiration of Hatch-

[37] FDA has previously expressed the view that it may approve a product based on the fact of the reference product's prior approval without relying on the trade secrets (e.g., safety and effectiveness data) underlying that approval. *See* Letter from Steven K. Galson, M.D., M.P.H., Director, CDER, to Kathleen M. Sanzo, Esq., Morgan, Lewis & Bockius LLP; Stephan E. Lawton, Esq., BIO; and Stephen G. Juelsgaard, Esq., Genentech, Docket No. 2004P-0231, PDN1 (May 30, 2006), at 38 n.70. This distinction, however, is artificial. For example, courts characterize abbreviated new drug applications (ANDAs) interchangeably as both applications that rely on FDA's prior findings, *see, e.g.*, *Andrx Pharms., Inc. v. Biovail Corp. Int'l*, 256 F.3d 799, 802 (D.C. Cir. 2001) (an ANDA "relies on the FDA's previous determination that the [innovator] drug is safe and effective"); *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1063 (D.C. Cir. 1998) (same), and applications that rely on the innovator's data, *see, e.g.*, *Purepac Pharm. Co. v. Torpharm, Inc.*, 354 F.3d 877, 879 (D.C. Cir. 2004) (an ANDA "'piggyback[s]' on the safety and effectiveness information that the brand-name manufacturer[] submitted in [its] NDA[]"); *Am. Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1079 (D.C. Cir 2001) ("a generic drug ANDA [can] rely on the pioneer NDA's safety and effectiveness studies"). Indeed, FDA has acknowledged that reliance on findings about an innovator NDA "is certainly indirect reliance on the data submitted in the original NDA." Letter from Janet Woodcock, M.D., Director, CDER, to Katherine M. Sanzo, Esq. & Lawrence S. Ganslaw, Esq., Morgan, Lewis & Bockius, LLP; Jeffrey B. Chasnow, Esq., Pfizer Inc.; Stephan E. Lawton, Esq. & Gillian R. Woollett, Ph.D., BIO; and William R. Rakoczy, Esq., Lord, Bissell & Brook LLP, Docket No. 2003P-0408, PDN 1 (October 14, 2003), at 10 n.14. As FDA's position makes a distinction without a difference, it does not save FDA action from constituting a taking of an applicant's property rights in its trade secrets.

[38] *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983).

[39] FDA has asserted that exclusivity is not a property right. *See, e.g.*, 59 Fed. Reg. 50338, 50339 (Oct. 3, 1994) ("New drug exclusivity is not a property right, but is rather a statutory obligation on the agency. . . . [T]here is no property right to exclusivity itself that can be transferred separately and apart from the application or data upon which exclusivity is based."); Letter from John Taylor, Assoc. Comm'r for Regulatory Affairs, FDA, to Patricia J. Kenney, Esq., Genentech, Inc., Docket No. 86P-0452 (Mar. 6, 1987) [hereinafter Genentech Letter], at 2 (with respect to orphan drug exclusivity, stating "[t]he seven-year period of exclusive marketing is not a property right but is a prohibition against action by FDA"). In defense of this position, FDA has stated that "a patent is distinguishable from exclusive marketing . . . in that patents are specifically recognized in the Constitution." Genentech Letter, at 2. That assertion disregards "the basic axiom that property interests are not created by the Constitution," but by "existing rules or understandings that stem from an independence source." *Monsanto*, 467 U.S. at 1001.

Waxman or pediatric exclusivity. The BPCIA transition provisions simply provide that in 2020 an approved application for a biological product under section 505 of the FDCA will be "deemed" a license under section 351 of the PHSA. For NDA applicants after enactment of the BPCIA, there may have been some uncertainty as to whether their post-transition exclusivity rights would be determined by the FDCA or the PHSA. But *both* of those regimes confer exclusivity rights; the statute certainly did not provide notice that FDA would honor *neither* form of exclusivity. Any applicant who submitted valuable trade secrets to FDA in connection with an NDA, and met the statutory criteria for exclusivity, could reasonably rely on having statutory exclusivity.[40]

FDA should avoid what at minimum are serious constitutional concerns with its proposed interpretation. As we explain below, the BPCIA is readily susceptible to an interpretation that does not prematurely extinguish an applicant's exclusivity rights.

D. *The Draft Guidance is inconsistent with U.S. free trade agreements.*

The Draft Guidance's proposal to extinguish Hatch-Waxman exclusivity for transition biological products is also inconsistent with hard-fought international trade protections in U.S. free trade agreements (FTAs). Under the World Trade Organization (WTO)'s Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), WTO members must protect certain test data against unfair commercial use when submission of such data is a condition of approving the marketing of pharmaceutical products that utilize new chemical entities.[41] Similarly, U.S. FTAs have provided that if a Party requires submission of information concerning the safety and efficacy of a new pharmaceutical product before permitting that product to be marketed, then the Party shall not permit third parties to market the same or a similar product for at least five years.[42] Notably, when implementing its trade agreements, the U.S. has not been required to change its domestic law in order to comply with these data protection obligations.[43]

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[40] *Monsanto*, 467 U.S. at 1006 (reasonable investment-backed expectations depend on whether the property owner is "on notice").

[41] *See* Agreement on Trade-Related Aspects of Intellectual Property Rights, at art. 39(3), Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, THE LEGAL TEXTS: THE RESULTS OF THE URUGUAY ROUND OF MULTILATERAL TRADE NEGOTIATIONS 320 (1999), 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994).

[42] *See, e.g.*, U.S. FTAs with Singapore (article 16.8), Korea (article 18.9), Chile (article 17.10), and Australia (article 17.10). These U.S. trade agreements require that the period of protection be "at least five years." Meanwhile, U.S. trade agreements with Colombia, Panama, and Peru require a period of "normally" five years, "taking into account the nature of the data and person's efforts and expenditures in producing them." *See* U.S. FTAs with Colombia (article 16.10), Panama (article 15.10), and Peru (article 16.10). The use of "normally" reflected a U.S. congressional-executive agreement, known as the "May 10th Agreement," to secure passage of these trade agreements, taking into account these particular countries' level of economic development.

[43] *See, e.g.*, United States-Korea Free Trade Agreement Implementation Act, Statement of Administrative Action ("No statutory or administrative changes will be required to implement Chapter Eighteen [on Intellectual Property Rights].").

The Office of the U.S. Trade Representative (USTR) has long touted the importance of the inclusion of such provisions in U.S. FTAs. In a 2003 prepared statement to Congress, Assistant U.S. Trade Representative for Asia, the Pacific, and APEC, Ralph F. Ives, III, described the U.S.-Singapore FTA's intellectual property provisions as "innovative and state-of-the art" and noted that these provisions would protect "confidential test data against unfair use for five years for pharmaceuticals."[44] USTR has also called out its trading partners that fail to provide this protection. In its 2015 Special 301 Report, for example, USTR stated that China's failure to provide effective protection of intellectual property, including pharmaceutical test data, accounts for the disproportionately low sales levels for intellectual property rights-intensive goods and services in China.[45]

By failing to honor five-year Hatch-Waxman exclusivity for some transition biological products, FDA's proposed approach runs counter to U.S. international trade obligations. For example, under the agency's proposal, applicants who qualified for and were granted five-year exclusivity under the FDCA before March 23, 2020 will lose some or all of that exclusivity without any comparable exclusivity award under the PHSA. In other words, these applicants will enjoy less than the five years of exclusivity due under the FTAs. The agency should revise the Draft Guidance to ensure U.S. compliance with these FTAs.

E. ***A more balanced approach would avoid these concerns.***

FDA should abandon its proposed approach to exclusivity for transition biological products. Instead, if a transition biological product application earned exclusivity in accordance with the NDA statutory requirements, the agency should continue to recognize this period of exclusivity following the transition date. More broadly, until expiry of every *Orange Book*-listed patent, including any pediatric exclusivity extension, for a given listed drug, FDA should continue to treat the application for that drug, as well as the follow-on applications that cite it, as section 505 applications for exclusivity and patent purposes.

This approach is consistent with the meaning of the word "deemed" as creating a legal fiction, which confers FDA the flexibility to implement an alternative approach to technical application of either statute. It also does not extinguish vested rights in exclusivity and therefore avoids the concerns identified above. Moreover, given that the patent litigation framework that applies to biological products under the FDCA is different from the framework set forth in the BPCIA,[46] this approach would be less disruptive to transition biological product

[44] *Trade in Services and E-Commerce: The Significance of the Singapore and Chile Free Trade Agreements, Hearing before the Subcomm. on Commerce, Trade and Consumer Protection of the H. Comm. on Energy and Commerce*, 18 (2003) (Prepared Statement of Ralph F. Ives, III, Ass't U.S. Trade Representative for Asia, the Pacific, and APEC).

[45] USTR, 2015 USTR Special 301 Report, at 32 (2015), https://ustr.gov/sites/default/files/2015-Special-301-Report-FINAL.pdf.

[46] *Compare* FDCA § 505(c)(3)(D) *and* FDCA § 505(j)(5)(C) *with* PHSA § 351(l).

sponsors, especially those engaged in ongoing Hatch-Waxman litigation to resolve patent disputes on March 23, 2020. Continuing to treat transition biological product applications as NDAs for intellectual property purposes for a limited time would reduce potential concerns about courts' loss of jurisdiction over such disputes (due to the lack of a section 505 application), among other things.[47]

Moreover, the described approach addresses FDA's concern, whether accurate or not, that Congress did not intend to "grant biological products approved under section 505 of the [FDCA]—some of which were approved decades ago—a period of exclusivity upon being deemed to have a license under the [PHSA] that would impede biosimilar or interchangeable product competition in several product classes until the year 2032."[48] Under our proposed approach, these transition biological products would only receive the balance of regulatory exclusivity due under Hatch-Waxman and any applicable pediatric extension. This approach strikes the appropriate balance in protecting the investments and vested interests of transition biological product sponsors while enabling follow-on applicants to enter the market in a timely manner.

III. FDA's Proposed Approach to Pending NDAs and Supplements is in Tension with the BPCIA and Would Impose Undue Burdens and Have Negative Public Health Consequences

As proposed in the Draft Guidance, NDAs for biological products that are pending on March 23, 2020—including those that have been tentatively approved—"will not be able to be approved" after the transition, and applicants may withdraw and resubmit their applications under the PHSA.[49] The agency reasons that section 7002(e)(4) refers only to conversion of "approved" NDAs and does not provide a mechanism for conversion of NDAs either prior to or after March 23, 2020, because it refers to conversion "on" March 23, 2020.[50] Although the Draft Guidance does not expressly address the issue, it seems that FDA's proposed approach to pending full applications is intended to apply equally to pending supplemental NDAs for

[47] *See* 35 U.S.C. § 271(e)(2)(A) ("It shall be an act of infringement to submit . . . an application under section 505(j) of the [FDCA] or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent, . . . if the purpose of such submission is to obtain approval under such Act to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent or the use of which is claimed in a patent before the expiration of such patent"). To the extent there is a loss of jurisdiction under section 271(e)(2)(A) due to the lack of a section 505 application, and this impairs the innovator's ability to enforce its patent rights—a property interest protected by the Takings Clause—we note that this too would raise a constitutional concern regarding an improper taking in violation of the Fifth Amendment. *See Adams v. United States*, 391 F.3d 1212, 1225–26 (Fed. Cir. 2004) (explaining that where a "cause of action protects a legally-recognized property interest," the Takings Clause operates to prevent impairment of the cause of action without just compensation).

[48] Draft Guidance, lines 210–14.

[49] *Id.*, lines 164–65.

[50] *Id.*, lines 151–55.

transition biological products, in light of the overall tone of the Draft Guidance and the fact that supplements are typically considered a type of application.[51]

FDA's position is contrary to the plain language of other provisions of the statute. The proposed approach also would be unduly burdensome and undermine public health interests. PhRMA urges the agency to adopt a different approach: NDAs and supplemental NDAs for transition biological products that are pending on the transition date should retain their status until FDA approval, and then immediately be deemed to be BLAs or supplemental BLAs, respectively, for purposes other than intellectual property rights.[52]

A. *FDA's proposal is inconsistent with the plain language of the BPCIA.*

Section 7002(e)(4) of the BPCIA cannot be read in isolation and, once the transition provisions are read together, it is clear that FDA's reading conflicts with the plain language of section 7002(e)(2).[53] As discussed above,[54] that provision states that an application for a transition biological product "*may be submitted*" under section 505 of the FDCA if it "is submitted to [FDA] *not later than* the date that is 10 years after [March 23, 2010]."[55] Congress therefore expressly provided that the NDA pathway would remain open for proposed transition biological products up to and until March 23, 2020. Indeed, where Congress wanted to restrict access to the NDA pathway during the ten-year transition period, it did so outright: a sponsor must use the BLA pathway if there is "another biological product approved under [PHSA section 351(a)] that could be a reference product . . . if such application were submitted under [PHSA section 351(k)]."[56]

Yet FDA's proposed interpretation would have the practical effect of foreclosing the NDA pathway for proposed transition biological products prior to March 23, 2020, in direct contradiction of Congress's express intent. By providing that the agency will not approve NDAs and apparently supplemental NDAs pending on the transition date, FDA is essentially forcing

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[51] *See, e.g.*, 21 C.F.R. § 314.3(b) (explaining that the term application "include[es] all amendments and supplements to the application").

[52] As FDA acknowledges in the Draft Guidance, there is no analog to section 505(b)(2) of the FDCA in the PHSA. *See* Draft Guidance, lines 254–55. PhRMA therefore agrees with FDA's proposal to require that all transition biological product applications meet the conditions of section 351(k) or else be a 351(a) application under the PHSA after the transition date.

[53] *See United States v. Morton*, 467 U.S. 822, 828, 104 S. Ct. 2769, 2773, 81 L. Ed. 2d 680 (1984) ("We do not . . . construe statutory phrases in isolation; we read statutes as a whole."); *see generally FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. at 133 ("A court must therefore interpret the statute 'as a symmetrical and coherent regulatory scheme,' and 'fit, if possible, all parts into an harmonious whole[.]'") (citations omitted).

[54] *See* section II.B.

[55] Pub. L. No 111-148, Title VII, Subtitle A, § 7002(e)(2), 124 Stat. 119, 817 (2010) (emphases added).

[56] *Id.* § 7002(e)(3).

innovators to choose the BLA pathway earlier than the statute requires. It is unlikely that Congress intended for the NDA approval pathway to remain open in form, but not substance, in the lead up to the transition date. But that is exactly the effect of FDA's interpretation. Absent the single, explicit statutory exception precluding its use,[57] the BPCIA is clear that the NDA pathway must remain available to transition biological product applicants until March 23, 2020—not March 22nd, not two months before, not ten months before, not two years before. FDA's proposed interpretation of section 7002(e)(4) thus does not align with section 7002(e)(2).

B. *FDA's proposal would impose undue burdens and have negative public health consequences.*

At best, FDA's proposal is highly burdensome on applicants; at worst, it is unworkable and harmful to the public health.

The mechanics of withdrawing and resubmitting pending applications—applications that could be deep into the review process on March 23, 2020—would be disruptive for both sponsors and the agency and would necessitate the dedication of significant resources to achieve what could be accomplished through a simple clerical change at the end of the review process. The agency's silence on user fees and review performance goals for transition biological products, as discussed below,[58] only adds considerable uncertainty to the burden sponsors of transition biological products are facing as March 23, 2020 draws near. For example, some supplements, such as changes-being-effected supplements, will have already been implemented but not yet "approved" on March 23, 2020. Whether such a supplement would still be considered "pending" and subject to withdrawal and resubmission under FDA's proposal is unclear, but if so this approach would be logistically problematic for sponsors.

Moreover, for applicants planning to seek approval of follow-on versions of biological products approved under NDAs toward the end of the transition period, the practical effect of FDA's proposal is a virtual "Catch 22." The innovator drugs that these applicants intend to cite as reference drugs will remain approved under NDAs until March 23, 2020; thus, these innovator products will not meet the statutory definition of "reference product" during the transition period.[59] Accordingly, the follow-on applicants would be unable to submit a biosimilar application before the transition date.[60] Indeed, FDA acknowledges as much: the

[57] *See id*.

[58] *See infra* section IV.

[59] *See* PHSA § 351(i)(4) ("The term 'reference product' means the single biological product *licensed under subsection (a)* against which a biological product is evaluated in an application submitted under subsection (k).") (emphasis added).

[60] *See id.* § 351(i)(2) ("The term 'biosimilar' or 'biosimilarity', in reference to a biological product that is the subject of an application under subsection (k), means—(A) that the biological product is highly similar to the *reference product* notwithstanding minor differences in clinically inactive components; and (B) there are no clinically meaningful differences between the biological product and the *reference product* in terms of the safety, purity, (continued…)

agency explains that would-be section 505(b)(2) applicants could modify their development programs to "support submission of a 351(k) BLA for a proposed biosimilar product or a proposed interchangeable product *at such time as there is a biological product licensed under section 351(a) of the [PHSA] that could be a reference product.*"[61] Yet, unless the applicants believe that they can obtain final approval before March 23, 2020, filing a section 505(b)(2) application does not appear to be a workable option either. While FDA could begin reviewing this application, that application could later need to be withdrawn and re-submitted as a BLA following March 23, 2020, potentially resulting in an additional user fee and new review clock (and potentially also re-starting related patent litigation[62]). In sum, these applicants would have no viable approval pathway until March 23, 2020.

For example, consider a sponsor who files a section 505(b)(2) application in 2018 where the reference listed drug (RLD), which was approved in 2014, has listed patents and five-year exclusivity. The 505(b)(2) sponsor files its application on the date four years after RLD approval and provides paragraph IV certifications to the listed patents, and the RLD sponsor timely initiates a suit for patent infringement; a 30-month stay of approval is triggered. Unless the 505(b)(2) sponsor can prevail in the infringement suit prior to the transition date—an unlikely proposition—there is no way the applicant can get final approval during the transition period. Thus, the 505(b)(2) sponsor is left with a choice that is no choice at all: the applicant can file its application under the NDA approval pathway, potentially be "stuck" for two years, and then be forced to re-submit the application under PHSA, or it could delay filing entirely for two years.

Similar concerns about a blackout period apply for supplemental NDAs for transition biological products. As noted, the Draft Guidance implies that FDA would not approve supplemental NDAs for transition biological products that are pending on March 23, 2020 and would require these supplements to be withdrawn and resubmitted under the PHSA (or else delayed altogether until the underlying NDAs are deemed BLAs). If this reading is correct, sponsors of transition biological products who wish to submit supplements in the last few years of the transition period also would find themselves in a virtual "Catch 22": filing an sNDA would not be a viable option because approval might not occur before the transition date, and submission of a supplement under the PHSA would not be feasible because a BLA supplement presumably cannot be submitted to an approved NDA.[63]

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and potency of the product.") (emphases added); *id.* § 351(k)(3)(A)(i) (providing that FDA shall license a biological product under subsection (k) if, among other things, FDA determines that the application shows that the product is "biosimilar to the reference product").

[61] Draft Guidance, lines 269–72 (emphasis added).

[62] *See supra* notes 46 and 47 and accompanying text.

[63] *See* 21 C.F.R. § 314.71(b) ("All procedures and actions that apply to an [NDA] under § 314.50 also apply to [NDA] supplements"); *id.* § 314.1(b) ("This part does not apply to drug products subject to licensing by FDA under the Public Health Service Act").

Significantly, the described blackout period for supplements would run counter to public health interests. Delaying supplements until after March 23, 2020 would unnecessarily postpone approval of new indications and improvements to existing products to the detriment of patients. FDA's proposal therefore could restrict patient choice and treatment options and hamper efforts by sponsors to improve products and ensure a consistent drug supply. The agency should be wary of embracing its proposed implementation approach given this likelihood and should look to an alternative approach that puts patient health and safety first.

C. *The proposed approach would avoid these concerns.*

A better approach would be for FDA to maintain the status of any NDA or supplement for a biological product that is pending on March 23, 2020 until its approval and then deem the approved application or supplement to be a BLA or BLA supplement for purposes other than intellectual property rights. This approach would be the least disruptive, as it would preclude the introduction of new substantive requirements for these applications in the midst of their review and thereby help to ensure the timely and efficient review of submissions. This approach is also desirable from a public health standpoint as, contrary to the agency's current proposal, it would not obstruct efforts by sponsors to improve their products and ensure a consistent drug supply.

FDA has ample discretion to adopt this approach. While the statute speaks only to approved NDAs transitioning "on" March 23, 2020, it does not foreclose FDA from also transitioning applications approved thereafter. As one court has said, "[w]e do not read the enumeration of one case to exclude another unless it is fair to suppose that Congress considered the unnamed possibility and meant to say no to it."[64] Unlike in section 7002(e)(2) of the BPCIA and section 351(k)(7) of the PHSA as discussed above, Congress did not specify any exceptions to the "deemed to be a license" provision or otherwise seek to limit its scope. There is thus no evidence that Congress considered the possibility that NDAs approved after March 23, 2020 could transition and meant to say no to it.[65] Moreover, this interpretation is more consistent with section 7002(e)(2), which preserves the right to submit an NDA "not later than" March 23, 2020.

[64] *Otsuka Pharm. Co., Ltd. v. Burwell*, No. GJH-15-852, 2015 WL 3442013, at *10 (D.D.C. May 27, 2015) (quoting *Barnhart v. Peabody Coal Co.*, 537 U.S. 149, 168 (2003)).

[65] *Cf. Hennepin Cnty. v. Fed. Nat. Mortgage Ass'n*, 742 F.3d 818, 821 (8th Cir. 2014) ("The existence of statutory exceptions indicates that Congress considered whether there was need for any exception and 'limited the statute to the ones set forth.'") (quoting *United States v. Johnson*, 529 U.S. 53, 58 (2000)).

IV. The Draft Guidance is Silent on Issues of Critical Importance to the Implementation of the BPCIA's Transition Provisions

The Draft Guidance fails to address several important issues for NDAs that will be deemed BLAs on the transition date. PhRMA encourages FDA to promptly address these issues, which include:

- **Whether applications under section 505 of the FDCA will be deemed BLAs under section 351(a) or section 351(k) of the PHSA**

Footnote 7 of the Draft Guidance indicates that the agency "intends to provide additional guidance regarding its approach for determining when an approved application for a biological product under section 505 [of the FDCA] will be deemed a license for the biological product under section 351(a) or 351(k) of the [PHSA] . . . ." Given that more than half of the transition period has already passed, FDA should make its position on this issue known on an expedited timeline. This transition will be particularly challenging for section 505(b)(2) applications given that, as FDA acknowledges, there is no analog to section 505(b)(2) of the FDCA in the PHSA.[66] Even though a section 505(b)(2) application is a reliance-based application similar to a section 351(k) application, a product subject to a section 505(b)(2) application may differ from its listed drug in dosage form, strength, route of administration, and conditions of use—differences that are not permitted for a section 351(k) application.[67] In short, section 505(b)(2) applications do not completely align with the requirements of either a section 351(a) or a section 351(k) application, and it is unclear how FDA intends to reconcile these discrepancies when these applications transition to BLAs.

What is clear, however, is that FDA's approach could have significant implications for transition biological product sponsors. For instance, whether an application is deemed licensed under section 351(a) or 351(k) of the PHSA may affect whether interchangeability provisions of the PHSA apply to the application,[68] as well as the applicable patent dispute resolution framework. So that stakeholders have adequate time to plan and prepare for these matters before the transition date, FDA should provide guidance on this issue promptly.

[66] *See* Draft Guidance, lines 254–55.

[67] See PHSA § 351(k)(2)(i)(III)–(IV) (providing that a biosimilar application must include information demonstrating that it has the same condition or conditions of use, route of administration, dosage form, and strength as the reference product).

[68] *See id.* § 351(k)(4) (providing safety standards for determining interchangeability and referring to subsection (k) applications only, not subsection (a) applications).

- **Listing of Transition Biological Products in the *Purple Book* and Treatment of Pre-Transition Therapeutic Equivalence Determinations in the *Orange Book***

FDA proposes to remove NDAs and ANDAs for biological products from the *Orange Book* on March 23, 2020 because, according to the agency, such products will no longer be "listed drugs" that may be referenced by a section 505(b)(2) or ANDA applicant.[69] But the agency does not address whether these products will be added to the Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations, also known as the *Purple Book*. While PhRMA believes that these products should *not* be removed from the *Orange Book* as described, failure to list these products in either publication is problematic. For example, the approval status of these transition biological products could appear uncertain if they are not included in at least the *Purple Book*, which could have ramifications for imported products where clarity about their approval status is necessary. Additionally, failure to list these products in either the *Orange Book* or the *Purple Book* will affect substitution practices under state pharmacy laws.[70]

FDA's proposal also does not address whether the agency will consider transition biological products listed as therapeutically equivalent in the *Orange Book* to be interchangeable with the reference product upon the transition. Nor does it address what standard will be used to establish substitutability and how it will apply after the transition date. Guidance is needed on these issues given the differences between the therapeutic equivalence criteria and the statutory interchangeability standard in the PHSA. For a product approved under the FDCA, a determination of therapeutic equivalence means that it and its reference listed drug are "pharmaceutical equivalents and . . . can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling."[71] By contrast, to satisfy the interchangeability standard in the PHSA, an applicant must show that the product is biosimilar and "can be expected to produce the same clinical result as the reference product in any given patient."[72] In the case of a multiple-use product, the applicant also must show that "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not

[69] Draft Guidance, lines 173–77.

[70] *See, e.g.*, 225 ILL. COMP. STAT. 85/19.5(a)–(b) (with respect to Illinois, providing that a pharmacist may substitute an interchangeable biological product for a prescribed biological product provided certain conditions are met, and defining "interchangeable biological product" to mean a product that FDA has licensed and determined meets the standards for interchangeability under the PHSA or has designated therapeutically equivalent as set forth in the *Orange Book*); TEX. OCC. CODE §§ 562.001(1-b), 562.008(b) (same, with respect to Texas).

[71] FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations* vii (36th ed. 2016) (*Orange Book*).

[72] PHSA § 351(k)(4)(A)(ii).

greater than the risk" of exclusive use of the reference product.[73] We encourage FDA to squarely address substitutability issues associated with the transition in guidance.

- **What administrative procedures will be involved in the deeming of an NDA to be a BLA**

For approved NDAs that will be deemed BLAs on March 23, 2020, the Draft Guidance is unclear as to what administrative procedures and steps will be involved in the deeming process. On the one hand, the Draft Guidance states that, on the transition date, transition biological product applications "will no longer exist" as NDAs and "will be replaced" by BLAs. This passage suggests that the sponsor will not need to make a new submission to the agency as part of the transition. On the other hand, footnote 7 of the Draft Guidance indicates that FDA intends to provide guidance on "administrative issues associated with the transition (including BLA numbers and user fee questions)." Based on this passage, it is unclear whether FDA believes user fees or some other administrative steps will be required. PhRMA firmly believes that additional user fees and FDA review should not be necessary to effectuate the deeming process and asks that FDA explicitly confirm this is the agency's intended approach. Given the late stage in the transition period, expedited guidance on these issues, as well as administrative and user fee issues for NDAs and sNDAs withdrawn and resubmitted as BLAs and sBLAs, is essential.

- **What technical requirements will apply to sponsors, manufacturers, and/or distributors of transition biological products after March 23, 2020**

FDA should directly address the technical requirements that will apply to transition biological product applications after March 23, 2020, particularly where the requirements for NDAs and BLAs differ. At the outset, we note that transition biological products have a history of safe and effective regulation under NDAs, and therefore, there is no urgent need for change to the applications' supporting materials. Indeed, consistency is in both the sponsors' and agency's interests, as it will be extremely burdensome for the agency to review an onslaught of application updates upon the transition or upon submission of a first supplement. PhRMA encourages FDA to issue guidance (or a proposed regulation) on this topic promptly, to ensure that appropriate stakeholder feedback can be obtained well in advance of the transition date. Specifically, PhRMA requests that FDA address the following issues.

1. *Continued ability to reference Type II Drug Master Files*

FDA states in the Draft Guidance that "a Type II Drug Master File (DMF) for a drug substance, drug substance intermediate, or drug product would not be acceptable for a BLA because a license holder is expected to have knowledge of and control over the manufacturing process for the biological product for which it has a license."[74] Although FDA states that it is

[73] *Id.* § 351(k)(4)(B).

[74] Draft Guidance, at 7 n.12.

considering a mechanism to allow NDAs that are deemed BLAs to continue to reference these DMFs, it also notes that this mechanism would apply in "limited circumstances."[75] Thus, it is largely unclear what would happen to approved NDAs that reference Type II DMFs upon the transition—including whether their approved status will come into question. Given the meaning of "deemed" as described above, FDA need not strictly apply the DMF requirements to NDAs that are deemed BLAs. Instead, FDA should apply a flexible approach to affected applications, clarify that their approved status will not be affected by DMF issues, and provide prompt guidance on steps sponsors should take to address remaining issues with reasonable timeframes for their execution.

2. *Postmarketing reporting and supplement requirements*

The Draft Guidance does not address how FDA will apply postmarketing reporting and supplement rules to transition biological products after March 23, 2020, given the differences between these requirements for BLAs and NDAs. Deviation reporting requirements for BLAs differ from NDA field alert reporting requirements in terms of standards for reportable issues, timing for notification, and to whom the report should be submitted.[76] Furthermore while adverse experience reporting requirements are largely similar for BLAs and NDAs, the BLA adverse experience reporting requirements apply to a broader group of entities than do the NDA reporting requirements.[77] With respect to supplements, the rules applicable to BLAs under 21 C.F.R. § 601.12 are similar to the rules for NDAs under 21 C.F.R. § 314.70, but again there are differences between the two. For example, the biologic product supplement rules place greater emphasis on validation of changes, changes in responsible personnel, and manufacturing changes.[78] Given these discrepancies and the history of safe and effective regulation of transition biological products under the NDA regulations, FDA should permit sponsors of these products to continue to comply with the NDA regulations in lieu of the BLA

[75] *Id.*

[76] *Compare* 21 C.F.R. § 600.14 *with id*. § 314.81.

[77] *Compare id.* § 600.80 *with id.* § 314.80. Under the biological product reporting requirements, the requirements apply to manufacturers, packers, and distributors—the same as for the NDA reporting requirements—but then also shared manufacturers, joint manufacturers, or any other participants involved in divided manufacturing.

[78] *E.g.*, *compare id.* § 601.12(a)(2) ("Before distributing a product made using a change, an applicant must assess the effects of the change and demonstrate through appropriate validation and/or other clinical and/or nonclinical laboratory studies the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product.") *with id*. § 314.70(a)(2)("The holder of an approved application under section 505 of the act must assess the effects of the change before distributing a drug product made with a manufacturing change.").

regulations for a period of time after March 23, 2020. FDA could accomplish this objective through enforcement discretion and/or waivers under 21 C.F.R. § 600.90.[79]

3. cGMP compliance and inspection procedures

Whereas cGMP regulations codified at 21 C.F.R. parts 210 and 211 apply to biological products and drugs, cGMP regulations codified under 21 C.F.R. parts 600–680 apply only to certain biologics. In connection with revising the Draft Guidance, FDA should state that it will exercise enforcement discretion for the cGMP requirements under 21 C.F.R. parts 600–680 for transition biological products for some period of time, to allow manufacturers to adjust to the new requirements.

4. *Application formatting and content requirements*

FDA should clarify its approach to the technical requirements concerning the formatting and content of applications for transition biological products, including the proposed label format and the inclusion of process validation data.[80] Furthermore, product samples may not have been required as part of the NDA submission but are required for BLAs.[81] Thus, FDA should clarify whether and when sponsors of approved transition biological products will be required to submit samples if they have not already done so.

Again, given the history of safe and effective regulation of transition biological products under the NDA regulations, PhRMA believes that FDA should exercise enforcement discretion with respect to sponsors who continue to comply with NDA requirements for a period of time after the applications are deemed BLAs. This approach would protect the public health while minimizing burden on sponsors and the agency.

- **How FDA intends to interpret the "first licensure" exception for new BLAs for transition biological products**

Footnote 11 in the Draft Guidance states that "[t]he applicability of section 351(k)(7)(A) and (B) of the [PHSA] to BLA supplements and subsequent applications filed by the same sponsor or manufacturer after March 23, 2020, will be governed by section 351(k)(7)(C) of the

[79] *See id*. § 600.90 (providing FDA may waive postmarketing reporting requirements, among other requirements, for BLAs upon a showing that the requirement is unnecessary or that an alternative submission fulfills the requirement's purpose, among other grounds).

[80] *See generally id*. § 314.90 (providing FDA may waive application content and format requirements, among other requirements, for NDAs upon a showing that the requirement is unnecessary or that an alternative submission fulfills the requirement's purpose, among other grounds).

[81] *Compare id.* § 314.50(e)(1) (for NDA submissions, explaining that "[u]pon request from FDA, the applicant shall submit samples") *with id.* § 601.2(a) (for BLA submissions, explaining that an applicant shall submit "sample(s) representative of the product for introduction or delivery for introduction into interstate commerce").

[PHSA]." But this does not address how NDAs deemed to be BLAs will be considered in the analysis of whether a subsequent application proposes the "first licensure" of a biological product. Nor does it address how approved NDAs for transition biological products will factor into the "first licensure" analysis for a new BLA submitted during the last four years of the transition period. For example, consider a new stand-alone application for a transition biological product that the sponsor has the option of submitting under the NDA or BLA approval pathways at present. The sponsor opts for the latter and submits a full BLA. The previously-approved NDA is not yet deemed to be a BLA. Thus, we believe it is not a prior license under section 351(a) that should factor into the "first licensure" analysis for the new BLA.

Sponsors need to understand what exclusivity would apply to their products under these circumstances. These critical issues are left unaddressed by the Draft Guidance despite their importance to product development planning and business decisions, and the Draft Guidance's proposal to cut off all remaining exclusivity under the NDA pathway. FDA should clearly and promptly address these questions, particularly given that the transition period is already more than half over.

- **What nonproprietary naming convention FDA intends to apply to transition biological products**

Absent from the Draft Guidance is FDA's proposed approach for nonproprietary naming of transition biological products. PhRMA provided detailed comments on this issue in response to FDA's Draft Guidance for Industry on Nonproprietary Naming of Biological Products, wherein we recommended that FDA treat transition biological products consistently with other biological products and apply the agency's proposed nonproprietary naming policy to them as well.[82] To do otherwise would add unnecessary complexity to the transition process and could lead to confusion in the healthcare community.

V. Conclusion

PhRMA has serious concerns with the Draft Guidance, because, among other things we believe that the agency is misinterpreting the BPCIA in a manner that would harm the incentives of sponsors to innovate and bring new treatments to patients. We strongly recommend that FDA reconsider its proposed interpretation of the transition provisions and

[82] *See* Comments of PhRMA to Docket No. FDA-2013-D-1543 (Oct. 27, 2015).

substantially revise the Draft Guidance on an expedited basis and well in advance of March 23, 2020. If you have any questions about PhRMA's comments, please do not hesitate to contact us.

Respectfully submitted,

/s/
David E. Korn
Vice President and Interim General Counsel

/s/
Jeffrey K. Francer
Vice President and Senior Counsel

/s/
Jocelyn B. Ulrich
Assistant Vice President, Science and Regulatory Advocacy