Abbott

Regulatory Policy and Intelligence
FDA Liaison Office
1700 Rockville Pike, Suite 310
Rockville, MD 20852

Tel. 301-822-9030
Fax 301-255-0090

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Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket Nos. FDA-2011-D-0602, FDA-2011-D-0605, and FDA-2011-D-0611: Draft Guidances for Industry on Biosimilars

Dear Sir or Madam:

Abbott Laboratories is a global, broad-based health care company devoted to discovering new medicines, new technologies, and new ways to manage health. Our products span the continuum of care, from nutritional products and laboratory diagnostics to medical devices, biological products, and pharmaceutical therapies.

Abbott appreciates this opportunity to share its views regarding the Food and Drug Administration's (FDA's) implementation of the Biologics Price Competition and Innovation Act of 2009 (BPCIA). We welcomed FDA's issuance of three draft biosimilar guidance documents on February 15, 2012, as well as the agency's other efforts to seek public comment on key issues since enactment. We also submitted written comments to FDA's Part 15 hearing docket in December 2010.

We generally support the comments filed by the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Biotechnology Industry Organization (BIO). Our comments are intended to provide additional detail regarding five topics mentioned in FDA's draft guidances or in prior Abbott and industry comments to FDA: (1) statutory and scientific considerations relating to use of a foreign comparator product, (2) interpretation of the exclusivity provisions, (3) ensuring the workability of the premarket patent litigation provisions, (4) the need to clearly differentiate between biosimilar applications and full BLAs, and (5) statutory and constitutional constraints on use of the trade secrets in the reference product application. Our comments are intended to help ensure that the agency implements the BPCIA in a manner that is consistent with the statutory language, the Fifth Amendment to the U.S. Constitution, and good public policy.

I. Use of a Foreign Comparator Product

In all three draft guidances, FDA discusses the potential use of data derived from comparing the proposed product to a foreign comparator product[1] to demonstrate that the proposed product is biosimilar to the U.S.-licensed reference product. We are concerned that the proposed approach in the draft guidances may not comport with FDA's statutory authority and may not adequately ensure a scientifically sound and robust biosimilarity exercise.

In FDA's biosimilar Q&A document, the agency lists factors that a biosimilar applicant will need to consider in order to use testing against a non-U.S.-licensed product to support a demonstration that the proposed biosimilar product is biosimilar to the U.S.-licensed reference product. One of the factors is "the scientific bridge between the non-U.S.-licensed product and the U.S.-licensed reference product, including comparative physico-chemical characterization, bioassays/functional assays." [2]

We read this passage to suggest that a biosimilar applicant may use data from certain studies involving a foreign comparator product after showing similarity between the foreign comparator and the U.S. reference product. As the agency itself has recognized, however, current analytical methods are not sufficient to adequately characterize and compare two biologics in order to show that they are the same.[3] The agency has also recognized that clinical trials may not be sensitive or large enough to reveal subtle differences between two biological products.[4] Accordingly, even the most rigorous scientific bridging study will be able to show merely that the foreign comparator product and the U.S. reference product are, at best, *highly similar*. It will not be able to establish that they are the *same*.

This fact makes the passage about use of data from a foreign comparator product in the draft guidance particularly troubling because the draft guidances state elsewhere that the biosimilar applicant will be tasked at each stage of its development program with identifying and addressing residual uncertainty about differences between its proposed biosimilar product and the U.S. reference product.[5] If the actual comparator is not the same as the U.S. reference product, then it is hard to understand how "residual uncertainty" about differences between the

[1] By "foreign comparator," we mean an innovative biological product licensed outside the United States. In the draft guidances and elsewhere, FDA also uses the phrase "non-U.S.-licensed product" to refer to such a product.
[2] FDA, Draft Guidance for Industry on Biosimilars: Q & As Regarding Implementation of the BPCI Act of 2009: Questions and Answers 8 (February 2012).
[3] *See, e.g.*, FDA, Draft Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product 4 (February 2012) ("Unlike small molecule drugs, whose structure can usually be completely defined and entirely reproduced, proteins are typically more complex and are unlikely to be shown to be structurally identical to a reference product. . . . current analytical methodology may not be able to detect all relevant structural and functional differences between two proteins."); Steven Kozlowski, M.D. et al., *Developing the Nation's Biosimilars Program*, 5 N. ENGL. J. MED. 385, 385-86 (Aug. 4, 2011) ("The complex structures of biologic products are usually not easily characterized . . . .").
[4] *See, e.g.*, FDA, Draft Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product 20 (February 2012) ("Rare, but potentially serious, safety risks (e.g., immunogenicity) may not be detected during preapproval clinical testing because the size of the population exposed likely will not be large enough to assess rare events.").
[5] *Id*. at 7 ("At each step, the sponsor should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product and identify next steps to try to address that uncertainty.").

proposed product and the U.S. reference product can be resolved through reliance on data from a foreign comparator. Perhaps an applicant can show biosimilarity to a foreign comparator product, itself shown highly similar to the U.S. reference product, but this is not, as a legal or as a scientific matter, what the BPCIA requires as a supportable basis for approval.

First, as a legal matter, the statute provides that a reference product is the "*single* biological product licensed under [a U.S. biologics license application (BLA)] against which" a proposed biosimilar "*is evaluated*."[6] Further, the agency may approve an application under section 351(k) only if the information submitted in the application shows that the proposed product is biosimilar *to the reference product*.[7] Although the statute permits an applicant to submit additional information including public information regarding "another biological product,"[8] the provisions just quoted clearly preclude that additional product from serving as the statutorily mandated reference product. The finding of biosimilarity necessary for approval must be based on studies evaluating the proposed product against the U.S. reference product. Therefore, as a matter of law, *any* data essential to approval of the application must derive from studies evaluating the proposed biosimilar against the *reference product*. The standard to apply is the same standard FDA uses when applying sections 505(c) and 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) in determining whether a new drug application (NDA) or NDA supplement will receive three-year exclusivity: FDA awards exclusivity if the application contains reports of new clinical investigations "*essential to the approval* of the application."[9]

Second, as a scientific matter, a proposed product that is biosimilar to a foreign product that is highly similar to a U.S. reference product cannot be inferred to be, itself, biosimilar to the U.S. reference product. An approach taken by FDA in the small molecule setting is instructive here. In that setting, the agency has historically maintained that multiple AB-rated generic versions of a single reference listed drug are considered generic versions of each other.[10] This follows from

[6] PHSA § 351(i)(4) (emphasis added).
[7] PHSA § 351(k)(3)(A)(i).
[8] PHSA § 351(k)(2)(A)(iii)(II).
[9] FDA has nearly thirty years of experience interpreting the "essential to approval" standard in the FDCA. *See, e.g.*, 21 C.F.R. § 314.108(a) ("*Essential to approval* means, with regard to an investigation, that there are no other data available that could support approval of the application."); *Upjohn Co. v. Kessler*, 938 F. Supp. 439 (W.D. Mich. 1996) (discussing 19-page memorandum prepared by Dr. Robert Temple, assessing whether intravenous study of minoxidil in hypertensive patients was "essential" to approval of a supplement for OTC use of minoxidil topically for treatment of hair loss). The "essential to approval" standard effectively imposes a "but for" test. In other words, "without these new clinical studies, FDA would not have sufficient information to conclude that the drug product or change to a marketed drug product for which the applicant is seeking approval is safe and effective." *See* 54 Fed. Reg. 28,872, 28,900 (July 10, 1989); *see also id*. ("Thus, to qualify for exclusivity, there must not be published reports of studies other than those conducted or sponsored by the applicant, or other information available to the agency sufficient for FDA to conclude that a proposed drug product or change to an already approved drug product is safe and effective."); 130 Cong. Rec. H9099, H9124 (daily ed. Sept. 6, 1984) (statement of Rep. Henry Waxman) (describing 3-year exclusivity as attaching where the new clinical tests "are a prerequisite to FDA approval").
[10] *See, e.g.*, FDA, Therapeutic Equivalence of Generic Drugs - Letter to Health Practitioners (Jan. 28, 1998), *available at* http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm073182.htm ("... FDA approved product labeling does not recommend that any additional tests need to be performed by the health care provider when a switch occurs from

the fact that one drug is generic to another when it has the *same* active ingredient.[11] Thus, in the small molecule setting, because products A and B are the same, and because products A and C are the same, products B and C are the same. By way of contrast, sameness is neither scientifically achievable nor legally required for biological products. And so even if product A is biosimilar to B, which is highly similar to C, it cannot be inferred that A is biosimilar to C.

In rare cases, it may be possible for a biosimilar applicant to show that the foreign comparator product is *the same* as the U.S. reference product – which would (as a legal and scientific matter) justify reliance on comparisons with that foreign product. A biosimilar applicant should establish that the U.S.-licensed reference product and the foreign comparator product, and any components thereof, were manufactured in the same facility, on the same lines, to the same specifications, during the same time period.[12] This information could effectively show that the U.S.-licensed reference product and any foreign comparator product are the *same* and justify the pivotal use of data from trials against the foreign product.

In some circumstances this information may not be publicly available. In these cases, the biosimilar applicant may not be able to demonstrate that the U.S. reference product and the foreign comparator product are the same. In such a case, this simply means that data from trials with a foreign comparator product cannot be used as essential support for approval of the biosimilar product. Nor may FDA use nonpublic information about the U.S.-licensed reference product to reach a conclusion regarding sameness, thus permitting pivotal use of those data. Indeed, FDA may not use non-public information regarding the U.S. reference product for any purpose, when reviewing a biosimilar application, and the biosimilar applicant may include in its application only publicly available information relating to the reference product.

II. Exclusivity

The agency's draft Q&A guidance briefly addresses exclusivity for innovator products by stating that a biologics license applicant may "include in its BLA submission a request for reference product exclusivity under section 351(k)(7) of the PHSA, and FDA will consider the applicant's assertions regarding the eligibility of its proposed product for exclusivity."[13] Because addressing the scope of exclusivity is critical to promoting transparency and certainty for both innovative and biosimilar biologic sponsors, we urge FDA to provide further detail about its interpretation of the exclusivity provisions. More specifically, we ask that FDA explain its view of the "first licensure" exception to exclusivity.

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a brand-name drug product to a generic equivalent drug product, from a generic equivalent to a brand-name product drug, or from one generic product to another when both are deemed equivalent to a brand-name drug product.").

[11] FDCA § 505(j)(2)(A) (requiring a generic drug to have the "same" active ingredient or ingredients as the listed reference drug); FDA, ORANGE BOOK vi-vii (32d ed. 2012). ("Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration . . . ").

[12] Abbott therefore agrees with FDA regarding the significance of "the relationship between the license holder for the non-U.S.-licensed product and BLA holder for the U.S.-licensed reference product, including whether the non-U.S.-licensed product, and/or any components thereof, are manufactured in the same facility(ies) as the U.S.-licensed reference product during the relevant time period." Q & A Draft Guidance, *supra* note 2, at 7.

[13] Q & A Draft Guidance, *supra* note 2, at 15.

The "first licensure" provision is drafted as a narrow exception to the default rule that a biosimilar application cannot receive final approval until twelve years after licensure of the reference product.[14] This provision denies a separate 12-year exclusivity term to:

> (i) a supplement for the biological product that is the reference product; or
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> (ii) 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.

The terms used in the first licensure provision are not defined in the statute.

Licensor, Predecessor in Interest, or Other Related Entity. Abbott agrees with other stakeholders that in determining whether a biologic sponsor is a related entity with respect to a prior sponsor, FDA should take an approach to this provision that is objective, easy to apply, and consistent with the policy goals of exclusivity.

The intent of the statutory exclusivity provisions is to reward with exclusivity only significant and resource-intensive biologic product development efforts. The "licensor, predecessor in interest, or related entity" language quoted above reflects Congressional intent to deny exclusivity to parties benefitting from shortcuts in biologic product development (*i.e.*, those parties who did not undertake significant and resource-intensive development programs). Such parties should be understood to include those entities with the ability to leverage prior data and approvals in a manner that meaningfully reduces the burden of developing and submitting a "subsequent" BLA application.

Accordingly, in determining whether an applicant is a licensor, predecessor in interest, or other related entity for the exclusivity provisions, FDA should focus on whether, by virtue of the corporate relationship, the subsequent applicant is able to avail itself of any shortcut to approval, *i.e.*, whether the subsequent sponsor may avoid any of the significant obligations it otherwise would have to shoulder in submitting an application for the subsequent product. Whether the relevant applicants are under common ownership or control is an important consideration in determining whether the subsequent applicant received a shortcut, because such a relationship suggests that the second applicant would have the right to rely on the data submitted by the first applicant.

Focusing on whether the subsequent applicant received a shortcut would effectuate the purpose of the statute by rewarding only significant biologic product development efforts, and it would be practical for FDA to administer. FDA is well-positioned to evaluate a BLA and determine whether the sponsor is relying on or benefitting from data in, or the prior approval of,

[14] PHSA § 351(k)(7)(A), (B).

a previously licensed product. In those instances, the agency can then evaluate whether such reliance is the result of any sort of corporate relationship, without having to identify at the outset what types of relationships would prevent an award of exclusivity.

Structural Modification; Change in Safety, Purity, or Potency. The second clause of the first licensure exception for new BLAs — section 351(k)(7)(C)(ii) — applies *only* if a "subsequent application filed . . . for . . . a modification to the structure of the biological product [ ] does not result in a change in safety, purity, or potency." This subclause does not allow FDA to consider whether the structural differences are significant or whether the clinical profile is significantly different or superior. A plain reading of the subclause indicates that *any* structural modification coupled with *any* clinical differences are sufficient to garner 12 years of exclusivity. Thus, for example, changes in the heavy chain terminal sequences and glycan structure profiles, as well as changes in glycosylation patterns, should be considered structural modifications for purposes of this subclause. And new indications, as well as any other differences in safety, purity, and potency, should be considered clinical differences.

Moreover, it is generally understood that it will be difficult — sometimes impossible — for biological product sponsors to demonstrate conclusively the relationship between structural differences and clinical differences. There will be instances where it will be easier to prove this causal relationship — such as where a simple addition to the molecule has extended the half-life of the therapy in question. But it would be peculiar to reward simpler structural modifications to biologics while denying exclusivity for products that are more fundamentally structurally different as well as clinically novel, simply because the causal connection between the structural modification and the clinical impact cannot be proven. The overall in vivo mechanisms of action may not always be definitively determined or understood, preventing a sponsor of a subsequent application from proving definitively that the structural differences exhibited by the new product directly result in the changed safety, purity or potency profile of the product. Thus, the absence of proving a direct causal relationship should not prevent the grant of exclusivity.[15]

Finally, we request that FDA provide greater certainty to applicants by providing an initial answer with respect to eligibility for exclusivity early in the product's development process. In particular, where eligibility for exclusivity turns on the relationship between the applicant and a prior BLA holder, rather than on the structure or safety, purity or potency profile of the proposed product, we see no justification for waiting until filing or approval to provide an answer. We suggest a decision in these cases immediately following the pre-IND meeting.

III. Patent Certification

As FDA acknowledges in its draft guidances, the statute "also establishes procedures for identifying and resolving patent disputes involving applications submitted under section 351(k) of the PHS Act."[16] Section 351(l)(2) of the PHSA, which is an essential first step in this process, states:

[15] The language of the statute does not require a causal link between the structural change and the change in safety, purity, or potency. As noted above in the text, the statute can be read as requiring the "subsequent application" (not necessarily the structural change) to "result in" a product with a changed safety, purity, or potency profile.
[16] Q & A Draft Guidance, *supra* note 2, at 3.

> Not later than 20 days after the Secretary notifies the subsection (k) applicant that the application has been accepted for review, the subsection (k) applicant —
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> (A) shall provide to the reference product sponsor a copy of the application submitted to the Secretary under subsection (k), and such other information that describes the process or processes used to manufacture the biological product that is the subject of such application; and
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> (B) may provide to the reference product sponsor additional information requested by or on behalf of the reference product sponsor.

As Abbott put forth in its December 2010 comments to FDA, FDA should ensure that biosimilar applicants comply with subparagraph (A).[17] Subparagraph (A) is the first in a series of steps that ultimately culminate in premarket litigation of relevant patents, during which the opportunity for a statutory injunction is granted to the reference product sponsor.[18] If the biosimilar applicant fails to provide its application and manufacturing information, the scheme would not be workable. Without the biosimilar application and manufacturing information, for example, a reference product sponsor would have difficulty preparing, as required by the law, the list of patents for which a claim of infringement could reasonably be asserted.[19] Moreover, the deadline for providing this list is "60 days after the receipt of the application and information under paragraph (2)," which cannot be calculated if the application was not provided.[20] But an even more fundamental problem would also occur: a reference product sponsor might not even know that a biosimilar application had been filed until the biosimilar reached the market.

The reference in section 351(l)(2) to both the biosimilar application *and* "other" manufacturing process information recognizes that there may be information relating to the biosimilar's manufacturing process (and thereby relevant to informing the reference product sponsor's decisions about patent enforcement) that is not included in the application.[21] This would include information placed before FDA by the biosimilar applicant — for example, through cross-references to another company's application or through citation to a drug master file (DMF) — as well as information not provided to the agency to review.[22] FDA's regulations broadly define manufacture as "all steps in propagation or manufacture and preparation of

[17] Abbott Laboratories, Comment, Docket No. FDA-2010-N-0477-0041 (Dec. 28, 2010). Other stakeholders also urged FDA to ensure that biosimilar applicants comply with this mandatory step. *See* Pharmaceutical Research and Manufacturers of America (PhRMA), Comment, Docket No. FDA-2010-N-0477-0036 (Dec. 27, 2010); The Biotechnology Industry Organization (BIO), Comment, Docket No. FDA-2010-N-0477-0035 (Dec. 27, 2010); Johnson & Johnson, Comment, Docket No. FDA-2010-N-0477-0037 (Dec. 27, 2010).

[18] 35 U.S.C. § 271(e)(4)(D).

[19] *See* PHSA § 351(l)(3)(A).

[20] *See id.*

[21] The contents of a biosimilar application include not only the documents provided to FDA, but also samples of the drug substance or drug product provided to FDA. *See* 21 C.F.R. § 601.2(a) (requiring a BLA to contain representative samples of the product).

[22] Abbott notes that the agency does not at this time intend to permit biosimilar applicants to use Type II DMFs (for drug substances, intermediates, material used in their preparation, and drug products). Quality Considerations Draft Guidance, *supra* note 3, at 10. We believe that information in other types of drug master files would need to be provided under section 351(l)(2) and that if the agency ever chooses to accept Type II DMFs, biosimilar applicants would need to find a way to provide the information in question to reference product sponsors.

products," including, but not limited to "filling, testing, labeling, packaging, and storage."[23] Manufacturing process information therefore includes information on all steps in the preparation of the product, including manufacturing steps conducted by a contract or other third-party manufacturer.

Allowing biosimilar applicants to skip the step of providing this information to the reference product sponsor would be inconsistent with Congressional intent in placing a premarket patent litigation scheme in the PHSA and related amendments in the Patent Act. The patent provisions were intended to balance an innovator's right to enforce its patents, on the one hand, with the desire that premarket patent litigation not unduly delay biosimilar approval, on the other hand.[24] Members of Congress clearly understood that section 351(l)(2) created an obligation on the part of biosimilar sponsors.[25] If biosimilar applicants skip the first step in the patent information exchange process, the premarket patent litigation process falls apart, thereby thwarting Congressional intent in creating section 351(l) in the first place.

In short, we request that the agency ensure that applicants comply with section 351(l)(2) by requiring those applicants to certify in their applications as follows:

> Pursuant to 42 U.S.C. §§ 262(l)(1)(B) and 262(l)(2), not later than 20 days after receiving notice that this application has been accepted for review, I will provide to the reference product sponsor a copy of this application and information that describes the process or processes used to manufacture the product that is the subject of this application.

FDA should adopt a refuse-to-file (RTF) policy for applications that do not contain this certification.[26]

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[23] 21 C.F.R. § 600.3(u).

[24] *See* Press Release, Chairman Senator Kennedy, Statement of Senator Edward M. Kennedy on the Biologics Price Competition and Innovation Act (June 27, 2007), *available at* http://help.senate.gov/newsroom/press/release/?id=eed35f32-9770-49db-8892-da8e931d41b7&groups=Chair ("The bill also establishes a new process for rapidly identifying patents that could be disputed between the brand company and the biosimilar applicant. It recognizes the inherent complexity of the patents on these intricate biological molecules, and it also expedites the patent resolution process. That process, like much of the rest of the bill, is a balance between competing concerns. The brand company must be able to assert its patent rights on all appropriate patents. But the process shouldn't be a roadblock for the approval follow-on products. This legislation strikes the appropriate balance. It includes incentives for both parties to seek expeditious resolution of patent issues, and it includes deterrents for all participants not to game the system."). This statement was made in reference to the biosimilar draft passed by the Senate Committee for Health, Education, Labor, and Pensions in June 2007, which would ultimately become the BPCIA.

[25] For example, Senator Enzi stated that "[t]he biosimilar applicant must provide its application and information about its manufacturing process to the brand company." Like the statement by Senator Kennedy in note 24, *supra*, Senator Enzi's statement was made in reference to the biosimilar draft passed by the Senate Committee for Health, Education, Labor, and Pensions in June 2007. *See* Press Release, Ranking Member Senator Enzi, Enzi Commends HELP Committee Approval of Legislation to Allow Follow-on Biologics, Protect Patient Safety (June 27, 2007), *available at* http://help.senate.gov/newsroom/press/release/?id=ceee5134-69db-41c4-8bb8-8ede7b1520ac&groups=Ranking

[26] If a biosimilar sponsor signed the certification, but then failed to comply with section 351(l)(2)(A), the sponsor could also be held liable for making a false statement to the government under 18 U.S.C. § 1001, which imposes fines, imprisonment, or both on individuals making false representations to a federal agency.

FDA has required similar certifications in circumstances where the statute places a mandatory future obligation on an applicant but does not explicitly require certification. For example, section 505(k) of the FDCA requires only that an applicant comply with the postmarket reporting requirements set by FDA.[27] Section 505(k) of the FDCA thus places an obligation on applicants that they must complete after their application is filed, just as PHSA section 351(l)(2) places a future obligation on biosimilar sponsors filing applications. Section 505(k) contains no reference to requiring applicants to certify future compliance in their applications. Yet the NDA and BLA application form requires all applicants to certify that they will comply with the adverse event reporting requirements in 21 C.F.R. Parts 314 and 600. The NDA and BLA form also requires applicants to certify that they will comply with the labeling and advertising regulations and good manufacturing practice (GMP) regulations, and these certification requirements are not found in statute.

IV. Maintaining the Integrity of the 351(a) Approval Pathway

A. The PHSA does not authorize FDA to approve abbreviated applications submitted under section 351(a).

In December 2011, an FDA official stated publicly that an applicant for a biological product that seeks to rely on FDA's findings for a previously licensed biological product must file a section 351(k) application, not a section 351(a) application.[28] This official also noted that the 351(a) pathway does not contain any provision permitting reliance on approval of another product.[29] Abbott agrees.

As an initial matter, section 351(a) does not authorize a biologics license applicant to rely on a prior approval of another product or on data submitted by a prior applicant. The statutory language clearly contrasts with the approach in product approval provisions administered by FDA that do authorize such reliance.[30] Moreover, section 351(k) already authorizes applicants to rely on the agency's prior approvals of other biologics. To permit such reliance under section 351(a) would render section 351(k) impermissibly duplicative and superfluous.[31] Approving applications under section 351(a) that implicitly or explicitly rely on a prior approval or data submitted by a prior applicant would also be inconsistent with FDA's many statements over the years that it lacks the legal authority to do so.[32]

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[27] FDCA § 505(k)(1) ("In the case of any drug for which an approval of an application filed under subsection (b) or (j) of this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe . . .").

[28] *FDA Envisions Distinct Difference Between Biologic, Biosimilar Pathways*, FDA WEEK (Dec. 23, 2011).

[29] *Id.*

[30] For example, section 505(b)(2) of the FDCA authorizes an applicant to rely on investigations "not conducted by or for the applicant," and section 505(j) directs the applicant to cite, and compare its proposed drug to, another drug "previously approved" as safe and effective.

[31] *See Nat'l Ass'n of Home Builders v. Defenders of Wildlife*, 551 U.S. 644, 668-69 (2007).

[32] *See, e.g., Assessing the Impact of a Safe and Equitable Biosimilar Policy in the United States: Hearing Before the H. Comm. on Energy & Commerce Subcomm. on Health*, 110th Cong. 20 (2007) (statement of Janet Woodcock, M.D.) ("[A]n abbreviated pathway, though, does not exist for copies of protein products that are approved under the

Reading the statute to permit these types of BLAs also would be inconsistent with the fact that the BPCIA reflects a compromise between two competing goals: facilitating competition in the biologics market, on the one hand, and protecting and promoting biotechnological innovation, on the other hand.[33] The regulatory pathway provisions enable the approval of biosimilars, and the exclusivity and patent provisions protect and promote innovation. Approving 351(a) BLAs that implicitly or explicitly rely on a prior approval or data submitted by a prior applicant would undermine this balance, because companies that submitted full license applications would have no meaningful guarantee of exclusivity against this type of follow-on application. Moreover, companies that submitted full license applications under 351(a) would have no mechanism for premarket enforcement of their patents against these follow-on applicants. Like the effective elimination of exclusivity, this too would reduce the incentive to innovate. Neither outcome is consistent with the goal of the BPCIA. It is thus inappropriate to construe the statute as permitting approval of this type of follow-on BLA.[34]

B. FDA approval of abbreviated applications submitted under section 351(a) would constitute a taking under the Fifth Amendment.

Because the PHSA does not authorize FDA to approve abbreviated applications submitted under section 351(a), and because FDA has repeatedly disclaimed any authority to approve such applications, the companies that own those prior approvals have a reasonable, investment-backed expectation that their property will not be used to support such approvals. Permitting this use of section 351(a) would disrupt these expectations and therefore constitute a taking under *Ruckelshaus v. Monsanto Co.*[35] As discussed in the citizen petition Abbott Laboratories filed on April 2, 2012, all innovative product sponsors who submitted their applications to FDA before enactment of the BPCIA (March 23, 2010) had reasonable, investment-backed expectations that the trade secrets in their applications would not be used to approve competing products.[36]

Public Health Service Act."); *The Generic Drug Maze: Speeding Access to Affordable Life-Saving Drugs: Hearing before the S. Special Comm. on Aging*, 109th Cong. 56 (2006) (statement of Sen. Clinton to FDA witness) ("Mr. Buehler, I recognize that the FDA has been very public about its belief that it does not have the legislative authority to develop a pathway that would allow the vast majority of generic biologics to enter the market").

[33] *See* PPACA § 7001(b) (sense of the Senate provision that the statute was meant to establish "a biosimilars pathway balancing innovation and consumer interests"). "Sense of Congress" provisions are relevant to legislative intent. *See Accardi v. Pennsylvania Railroad Co.*, 383 U.S. 225, 229 (1966). The title of the statute — the Biologics Price Competition *and* Innovation Act — underscores its twin goals.

[34] *See Bob Jones Univ. v. U.S. Goldsboro Christian Schs., Inc.*, 461 U.S. 574, 586 (1983) (noting that the Supreme Court will construe statutes "in connection with . . . the objects and policy of the law") (emphasis, internal quotation marks, and citations omitted); *United Savings Ass'n of Tex. v. Timbers of Inwood Forest Assocs., Ltd.*, 484 U.S. 365, 371 (1988) ("A provision that may seem ambiguous in isolation is often clarified . . . because only one of the permissible meanings produces a substantive effect that is compatible with the rest of the law.") (citations omitted).

[35] 467 U.S. 986, 1011 (1984) ("If EPA . . . were now to disclose trade-secret data or consider those data in evaluating the application of a subsequent applicant in a manner not authorized by [statute], EPA's actions would frustrate Monsanto's reasonable investment-backed expectation with respect to its control over the use and dissemination of the data it had submitted.").

[36] *See* Docket No. FDA-2012-P-0317. Given these reasonable, investment-backed expectations, FDA approval of a biosimilar citing a reference product for which the BLA was submitted to FDA prior to enactment of the BPCIA would constitute a taking. Abbott's comments to this docket should therefore be interpreted as relating only to the agency's authority to approve biosimilars of post-enactment reference products.

Likewise, innovative product sponsors who submit BLAs *after* enactment *also* have reasonable investment-backed expectations – that their trade secrets will not be used to approve follow-on products under section 351(a). If FDA were to approve a follow-on biologic product under PHSA section 351(a), these expectations would be frustrated, and FDA and the government would be liable to providing the aggrieved sponsor with "just compensation" under the Fifth Amendment.

For all of these reasons, Abbott requests that FDA adopt procedural guidance that: (1) states that the agency will refuse to file any application submitted under section 351(a) of the PHSA that explicitly or implicitly relies on FDA's finding that another sponsor's previously approved biologic is safe, pure, and potent; and (2) describes the criteria FDA will use to determine when a BLA seeks to rely on a reference product for approval. We recommend that FDA assume that a BLA application seeks to rely on a reference product and should be filed under 351(k) if any of the following conditions is met:

- *The application contains comparative analytical data*. Showing structural similarity to a previously approved active ingredient, drug substance, or drug product is unnecessary in a non-abbreviated, stand-alone BLA. These data, however, are an essential component of any biosimilar application.[37] Including comparative analytical data therefore means that the applicant is seeking to abbreviate its development program by relying on a similarity between products (and thus, on an FDA finding of safety, purity, and potency for an earlier approved product).
- *The proposed product has been approved as a biosimilar in another country*. Biosimilar companies intend to prepare applications that can be submitted, perhaps with modest amounts of bridging data, in more than one jurisdiction. FDA has also announced that it will facilitate approval of biosimilars in the United States that have previously been approved abroad.[38] For this reason, prior submission of a similar application under a biosimilar pathway, or prior approval of the product as a biosimilar, in another country strongly suggests the applicant is seeking to rely, in some way, upon FDA's prior approval of another product.
- *The analytical segment of the application relies on a compendial or similar standard, most of the preclinical and clinical data are comparative, and the reference product has unexpired exclusivity*. In some cases, an applicant seeking to rely on a prior approval might omit comparative analytical data, theorizing that it can rely on compliance with a

[37] *See, e.g.*, Scientific Considerations Draft Guidance, *supra* note 4, at 7 (explaining that "extensive structural and functional characterization of both the proposed [biosimilar] product and the reference product . . . serves as the foundation of a biosimilar development program"); EMA, Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues, EMEA/CHMP/BWP/49348/2005 (2006) ("In order to provide assurance that the molecular structure of the active substance present in the similar biological medicinal product can be considered comparable to that in the reference medicinal product, it is generally necessary to conduct appropriate comparative tests at the level of the active substance.").

[38] *See* Biosimilar Biological Products, Presentation by Rachel E. Sherman, Associate Director for Medical Policy, Center for Drug Evaluation and Research, at slide 12 (explaining that biosimilar development programs include prospective development programs and "Retrospective" development programs — i.e., "Programs seeking licensure in US for similar biological products licensed outside the US").

compendial or similar standard for the key structural characteristics of the innovative product.[39] In these cases, FDA will need to use other indicia to determine whether the applicant is implicitly seeking to leverage a prior FDA approval. Substantial comparative data, coupled with unexpired exclusivity for the innovative product, might suggest the applicant is trying to rely on an innovative product's prior approval while circumventing the innovator's exclusivity.

The guidance could add that if FDA determined that an application triggered any of these presumptions, the agency would communicate this finding to the applicant. The applicant could then have a meaningful opportunity to demonstrate that it does not seek to rely on the prior approval of another company's product or on another company's trade secrets. In situations where the applicant could not overcome the presumption, however, FDA would refuse to file the application under section 351(a) and would instruct the applicant to file under section 351(k) or submit additional data so as to support a full 351(a) application.

V. Use of Reference Product Sponsor Trade Secrets

Under section 351(k) of the PHSA, a biosimilar applicant may cite only information about the reference product and its approval that is publicly available. The language in section 351(k) contrasts sharply with other language in the statutes administered by FDA that explicitly authorize the agency to rely on and use information in one company's application to approve a competitor's application.[40] For example, section 520(h) of the FDCA states that "[a]ny information contained in an application for premarket approval" of a device "shall be available, 6 years after the application has been approved by" FDA "for use" in "*approving another device*" and taking other regulatory actions.[41] Nothing in the BPCIA, by way of contrast, authorizes the reliance on, disclosure, or use of the actual trade secrets in the innovator's application, by the applicant or the agency.

Abbott is concerned, however, that the agency might unintentionally, inadvertently, but nevertheless impermissibly use and/or disclose to a biosimilar applicant innovator trade secrets if the reviewers who worked on the reference product BLA provide advice to the biosimilar applicant or review the biosimilar application — even if those individuals do not directly consult the reference product BLA and indeed even if (as we expect would be the case) they attempt to

[39] Compliance with compendial or similar reference standards is unlikely to be sufficient, standing alone, to satisfy the analytical requirements of the BPCIA. Abbott therefore supports the statement in the Draft Guidance on Quality Considerations that analytical studies should be part of a "broad comparison that includes, *but is not limited to*, the proposed biosimilar product, the reference product, applicable reference standards, and consideration of relevant publicly available information." Quality Considerations Draft Guidance, *supra* note 3, at 14 (emphasis added). *See also* 57 Fed. Reg. 17,950, 17,959 (Apr. 28, 1992) (noting that compliance with a USP monograph can help support a claim of sameness for ANDA approval, but that the agency may on a case-by-case basis "prescribe additional standards that are material to the ingredient's sameness").

[40] The direction to rely only on publicly available information must be viewed as deliberate. An earlier bill would have instead permitted "an abbreviated application for a license of a biological product that relies in part *on data or information in an application* for another biological product licensed under [section 351 of the PHSA] or approved under section 505 of the [FDCA]." H.R. 1427, 111th Cong. § 2 (2009) (emphasis added). A companion bill in the Senate contained identical language. S. 726, 111th Cong. (2009). These bills were rejected in favor of the approach that appears in the enacted law.

[41] FDCA § 520(h)(4) (emphasis added).

compartmentalize what they knew about the reference product. This disclosure could occur in many different ways, including implicit disclosures that come in the form of the questions that FDA asks of a biosimilar applicant.

FDA has itself acknowledged that it is impossible to eliminate a reviewer's knowledge of information in a prior application, stating in a Senate hearing on biosimilars that "reviewers are sometimes *unavoidably conscious* of information in a prior application, even without physically consulting the application, simply because they recall the information from having worked on the earlier review."[42] An analogous scenario involves employees who have knowledge of trade secrets and then become involved with new processes or products that are substantially similar to the product or process to which those trade secrets pertain.[43] Courts are sometimes called to adjudicate the risk of trade secret violation in this situation, and these courts have found that the likelihood that a party will use trade secret information for its own or another's benefit, and to the detriment of the trade secret owner, warrants issuing an injunction to protect against trade secret disclosure.[44] The courts reason that where an employee has detailed knowledge of trade secrets and is engaged in activity related to those trade secrets, unless he "possessed an uncanny ability to compartmentalize information, he would necessarily be making decisions about [new products] by relying on his knowledge of [the plaintiff's] trade secrets."[45] Although those cases emerge in a very different setting, and although we believe FDA scientists — as government employees — would strive to follow the law as drafted and protect innovator trade secrets, we believe this law regarding "inevitable disclosure" applies to the review of biosimilar applications.

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[42] *The Law of Biologic Medicine: Hearing Before the Senate Committee on the Judiciary*, 108th Cong. 66 (2004) (written statement by Lester M. Crawford, D.V.M., Ph.D., Acting Commissioner of Food and Drugs) (emphasis added).

[43] *See, e.g., Huawei Technologies Co. v. Motorola, Inc*., 2011 WL 612722, at *9 (N.D. Ill. Feb. 22, 2011) ("A plaintiff may prove a claim of threatened misappropriation of trade secrets by demonstrating that new employment will inevitably lead employees to rely upon trade secrets gained during their previous employment."); *Lombard Medical Technologies, Inc. v. Johannessen*, 729 F. Supp. 2d 432, 442 (D. Mass. 2010) (holding that "it is impossible to imagine" that former employees would not use, "consciously or not," confidential or proprietary information learned during their time at their former employer while working at their new job for a competitor); *YCA, LLC v. Berry*, 2004 WL 1093385, at *16 (N.D. Ill. May 7, 2004) (holding that the plaintiff's former employee "could not avoid" using the plaintiff's confidential information while performing the same marketing duties for his new employer); *Lumex, Inc. v. Highsmith*, 919 F. Supp. 624, 631 (E.D.N.Y. 1996) (holding that, notwithstanding the former employee's good intentions, it was inevitable that he would disclose his former employer's trade secrets in his new job working for his former employer's competitor because "[h]e cannot eradicate [those] trade secrets . . . from his mind").

[44] *Bimbo Bakeries USA, Inc. v. Botticella*, 613 F.3d 102, 113 (3d Cir. 2010) (affirming the grant of a preliminary injunction enjoining a former executive from working for a direct competitor because of the threat of disclosure of the former employer's trade secrets); *Huawei Technologies Co.*, 2011 WL 612722, at *11 (invoking the inevitable disclosure doctrine to preliminarily enjoin the threatened misappropriation of trade secrets); *Indus. Insulation Group, LLC v. Sproule*, 613 F. Supp. 2d 844, 855 (S.D. Tex. 2009) ("Injunctive relief may be necessary and appropriate 'even where there is no indication that a defendant and/or a former employee have benefited from the former employer's trade secret, where an employee is employed in a position that will result in inevitable disclosure of a former employer's trade secrets.'") (citations omitted); *Payment Alliance Int'l, Inc. v. Ferreira*, 530 F. Supp. 2d 477, 485 (S.D.N.Y. 2007) (preliminarily enjoining a former employee from working for a competitor because of the risk of inevitable disclosure of trade secrets).

[45] *PepsiCo, Inc. v. Redmond*, 54 F.3d 1262, 1269 (7th Cir. 1995).

Abbott therefore requests that FDA adopt formal safeguards to ensure that the trade secrets in reference product BLAs are not disclosed or used during biosimilar product development meetings, other communications with biosimilar sponsors, or review of biosimilar applications. A mere commitment by the agency not to use or disclose trade secrets and to consider only appropriate information when engaged in these activities is, in our view, insufficient to protect confidential information where disclosure is inevitable as a matter of law. Indeed, courts have consistently held that agreements of this sort "do not supplant the trade secret laws" and are "insufficient to prevent inevitable disclosure and use."[46] Agreements are particularly inadequate where, as here, employees will "be constantly called upon to decide" what they can properly rely on or disclose.[47] Moreover, agency policies regarding access to reference product applications have not always been effective in preventing reviewers from improperly accessing reference product applications,[48] or in preventing FDA employees from improperly accessing trade secret information more generally.[49]

We suggest the following safeguards in particular:

- Employees who were significantly involved in reviewing a particular reference product BLA and who have meaningful knowledge of the trade secrets in the BLA should not be permitted to participate in any biosimilar application review activities or any communications with a potential biosimilar applicant seeking to rely on that reference product.
- FDA should maintain an electronic database of employees involved in reviewing BLAs and biosimilar applications. This will allow the agency to provide notice to the BLA review team when a company is interested in creating a biosimilar of the reference product or has filed such an application.
- FDA should implement electronic safeguards to ensure that biosimilar application reviewers are not able to access the reference product BLA or other agency documents related to review of the BLA.
- The agency should create a manual of policies and procedures describing the safeguards above and others that may be appropriate and the purpose behind them.
- All agency employees involved in review of BLAs or biosimilar applications (or in development discussions related to innovative biologics or biosimilars) should be given training on these safeguards and the policies and procedures.

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[46] *PepsiCo, Inc. v. Redmond*, 1996 WL 3965, at *21 (N.D. Ill. Jan. 2, 1996) (collecting cases); *see also Huawei Techs. Co., Ltd.*, 2011 WL 612722, at *9 ("Contractual prohibitions against disclosure of trade secrets are routinely rejected as insufficient to prevent inevitable disclosure or use.").

[47] *FMC Corp. v. Varco Int'l, Inc.*, 677 F.2d 500, 504 (5th Cir. 1982).

[48] *See, e.g.*, Federal Defendants' Motion for Stay of Proceedings at 3, *Pfizer v. FDA*, No. 03-2346 (D.D.C. Feb. 18, 2004) (noting that FDA had belatedly discovered that an employee reviewing a 505(b)(2) application had considered the data in the Pfizer NDA for Norvasc during his review).

[49] Kendall, Brent, *Former FDA Chemist Admits Fraud*, WALL ST. J. (Oct. 19, 2011) (reporting that a former FDA chemist pled guilty to insider trading "based on confidential drug-approval information he accessed while at the agency").

- FDA should periodically review and issue public reports on the effectiveness of these safeguards and others that the agency uses to protect trade secrets more generally.

These safeguards are not intended to prevent FDA from accessing the application of the reference product sponsor to identify safety concerns when determining whether to let a biosimilar IND take effect and when deciding whether to approve a biosimilar licensure application. The agency should be free to ensure that any safety problems associated with the innovator's molecule have been adequately addressed, as appropriate, by the biosimilar applicant. So long as the reference product BLA is accessed solely to ensure patient safety and not to benefit the biosimilar applicant through additional shortcuts, this use of the innovator's trade secrets does not raise a takings concern. In order to ensure that the reference product BLA is not accessed in order to provide a competitive advantage to the biosimilar applicant, however, the BLA should be accessed only in limited circumstances to ascertain whether there are any lingering safety issues or gaps in data provided by the biosimilar applicant that should prevent the product from being initially studied in clinical subjects or licensed.

Abbott also recognizes that requiring complete separation of responsible personnel at every level of the agency would be infeasible. In some circumstances, a supervisor that approved licensure of the reference product BLA may be required to approve licensure of the biosimilar. The proposed institutional safeguards are intended to ensure that those FDA employees that are significantly exposed to the trade secrets in an innovator BLA are not placed in situations in which it is likely that they would inadvertently use or disclose to a biosimilar applicant those trade secrets. The specific employees may vary depending on how FDA structures the biosimilar review teams, but we would expect it to include, at a minimum, employees directly involved in the review of the chemistry, manufacturing, and controls and quality sections of the innovator BLA, as well as other line reviewers and project managers with direct and substantial access to confidential and trade secret information present in the innovator BLA.

These institutional safeguards will help to ensure that FDA complies with the language of the BPCIA. But they are also necessary to ensure that FDA avoids a taking of innovator property under the Fifth Amendment to the U.S. Constitution. Because the statute does not authorize FDA to disclose or use the trade secrets in the reference product BLA, reference product sponsors have a reasonable investment-backed expectation that FDA will not access the contents of their applications, use those contents to support advice to biosimilar applicants or approval of biosimilar applications, or disclose the contents (even inadvertently) to biosimilar applicants. Under *Monsanto*, therefore, accessing a reference product application's contents or using these contents as part of the biosimilar review or development process would disrupt innovator expectations.[50] This, in turn, would constitute a taking of the company's trade secrets, which would require just compensation under the Fifth Amendment.[51]

[50] 467 U.S. at 1010-11.

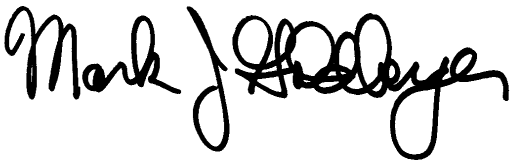
[51] The statute authorizes FDA to rely on its prior finding that a reference product was safe, pure, and potent — not on the trade secrets that supported the finding. As explained in our citizen petition, *supra* note 36, reliance on the finding for the benefit of a competitor uses the underlying trade secrets in a way that implicates the takings clause of the Fifth Amendment. This is because: (1) reliance on the finding inflicts a competitive harm on the trade secret owner, (2) reliance on the finding relieves the competitor from submitting similar amounts of data, and (3) the

The safeguards discussed above will also help achieve other ends, including helping to ensure FDA compliance with the Federal Trade Secrets Act, which prohibits the disclosure of trade secrets made known to a federal employee during his or her course of employment at a federal agency.[52] The proposed institutional safeguards (in particular, the training regarding trade secrets and the restricted access to BLA files) will help to ensure that agency employees do not inadvertently access trade secrets, which could lead to unintended disclosures. And by limiting the agency employees who have access to any specific confidential information, these safeguards should also help the agency with its efforts to police compliance with federal securities laws. We also believe that the institutional safeguards would avoid accidental and purely subconscious bias on the part of reviewers – somewhat like the double blinding that is required for a clinical trial to be viewed as adequate and well-controlled.[53]

VI. Conclusion

We appreciate the opportunity to submit these comments. Should you have any questions, please contact Ms. Lauren Hetrick at lauren.hetrick@abbott.com or by phone at (301) 822-9016 or Mr. Neal Parker at neal.parker@abbott.com or by phone at (202) 378-1424.

Sincerely,



Mark J. Goldberger MD, MPH
Divisional Vice President
Regulatory Policy & Intelligence
Abbott

finding and the underlying data supporting the finding are inseparable. Nevertheless, we believe that innovators submitting new BLAs are now on notice, under *Monsanto*, that their trade secrets will be used precisely as described in the BPCIA – indirectly (through reliance on the *approval* of their product rather than the *actual trade secrets* in their applications). Such use of innovator data submitted to FDA after the date of BPCIA's enactment does not raise the Constitutional Fifth Amendment takings issues that we assert exist with respect to pre-BPCIA BLAs, as fully discussed in Abbott's citizen petition.

[52] 18 U.S.C. § 1905.

[53] *See, e.g.*, FDA Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials § 1.2.2 (May 2001) ("Blinding is intended to minimize the potential biases resulting from differences in management, treatment, or assessment of patients, or interpretation of results that could arise as a result of subject or investigator knowledge of the assigned treatment.")