



## Evergreening Biologics

**ABSTRACT:** Discusses the data exclusivity provisions of the Biologics Price Competition and Innovation Act of 2009 (the “Biologics Act”), as well as Congressional intent to avoid “evergreening” of biologic drug products. Concludes that the FDA should deny any “new” period of data exclusivity when an application relating to a structurally modified reference product does not demonstrate, through “full clinical safety and efficacy data” that differences in “safety, purity, or potency” exist in a “second generation” product that are both “clinically meaningful” and patient favorable.

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Evergreening or “life cycle management” is a process used by pharmaceutical patent owners “to effectively extend the term of those patents by obtaining related patents on modified forms of the same drug, new delivery systems for the drug, new uses of the drug, and the like.”<sup>1</sup> Pharmaceutical patent owners have often employed a number of evergreening strategies, designed to “maximize their monopoly period,”<sup>2</sup> free from generic competition. At least since enactment of the Hatch-Waxman Act in 1984,<sup>3</sup> concern about the effect of evergreening strategies on the market price of pharmaceutical products and the overall cost of health care has been a central concern of consumers, regulators and legislators.

The same concern exists as a result of the recent enactment of the Biologics Price Competition and Innovation Act of 2009 (the “Biologics Act”), as part of the Patient Protection and Affordable Care Act, commonly known as the Healthcare Reform Act. Included in the legislation was a grant of “statutory authority to the Food and Drug Administration to license both “biosimilar” and “interchangeable” follow-on biologics. Also included in the legislation was language that, despite efforts to avoid evergreening,<sup>4</sup> may provide fertile ground for evergreening strategies.

The new Biologics Act endows the FDA with authority to issue general or specific guidance, after opportunity for public comment, including guidance about the criteria that the FDA will use to determine whether a biological product is “highly similar,”<sup>5</sup> and may thus be regarded as “biosimilar,” and criteria for determining whether a follow-on product is “interchangeable” with a “reference product.”<sup>6</sup>

#### *The FDA’s Notice and Request for Comments About A Biologics Pathway*

In October 2010, the FDA published a Notice and Request for Comments concerning certain “specific issues and challenges associated with the implementation of the Biologics [Act].”<sup>7</sup> In that Notice, the FDA recognized that the objectives of the [Biologics] Act are conceptually similar to those of the ...‘Hatch-Waxman Act’ ... which established abbreviated pathways for the approval of drug products...”<sup>8</sup> The Notice stated that the Biologics Act “aligns with FDA’s longstanding policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources and avoiding unnecessary duplication of human or animal testing.” However, the Notice added, because “[m]ost biological products are produced in a living system such as a microorganism, or plant or animal cells, whereas small molecule drugs are typically manufactured through chemical synthesis,” the FDA’s “implementation of an abbreviated approval pathway for biological products can present challenges given the scientific and technical complexities that may be associated with the

larger and often more complex structure of biological products, as well as the processes by which such products are manufactured.”

In its Notice and Request for Comments, the FDA of course sought “input regarding the agency’s implementation of the statute,” including, for example, input about the “scientific and technical factors should the agency consider in determining whether the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components.” In addition, because the Biologics Act also includes provisions relating to exclusivity, the terms of which in some respects parallel the statutory authorization of FDA approval of “biosimilars” and “interchangeables,” the Notice also sought comments about factors the agency should “consider in determining whether a modification to the structure of the licensed reference biological product results in a change in safety, purity, or potency, such that a subsequent BLA may be eligible for a second 12-year period of *marketing* exclusivity.”<sup>9</sup> The FDA’s inclusion of this topic exhibits concern about the manner in which the Biologics Act provisions might be used to engage in biologics evergreening. It also reflects a basic misunderstanding of the nature of the exclusivity created by the Biologics Act.

#### *Data Exclusivity, Not Marketing Exclusivity*

The structure and language of the statute does *not* provide for “marketing exclusivity,” as the FDA’s notice suggests. Instead, it provides for “data exclusivity.” The Biologics Act provides that “Approval of an application under this subsection may not be made effective by the Secretary until the date that is 12 years after the date on which the reference product was first licensed ... .”<sup>10</sup> It also provides that “An application under this subsection may not be submitted to the Secretary until the date that is 4 years after the date on which the reference product was first licensed ... .”<sup>11</sup> While the words of these sections are not identical to those used in comparable portions of the Hatch-Waxman Act,<sup>12</sup> they were modeled on those sections. Just as in the Hatch-Waxman context, any manufacturer may, after the initial period of 4 years, submit an application to the FDA for approval of a product that is “biosimilar” to or “interchangeable” with a reference product.<sup>13</sup> After that 4 year period, the FDA may consider the application, relying upon data previously submitted by the reference product sponsor, as well as certain statutorily prescribed information, within the discretion of the FDA,<sup>14</sup> but it may not approve an application until the expiration of 12 years after the date on which the reference product was first licensed.<sup>15</sup>

In a manner similar to the Hatch-Waxman Act,<sup>16</sup> the new Biologics Act provides that the FDA “shall license” a proposed biosimilar or interchangeable product if it finds that the proposed product “is biosimilar to the reference product” or meets statutory standards and is “therefore interchangeable with the reference product.”<sup>17</sup> Hence, like comparable provisions in the Hatch-Waxman Act, the Biologics Act does not explicitly state that, in reviewing a follow-on biologic product application the FDA is permitted to review and rely upon clinical and other data submitted in connection with a “reference product” Biologic License Application. Nevertheless, the language and legislative history of the Biologics Act also make clear that, in comparing a follow-on to a reference biologic product to determine biosimilarity or interchangeability, access to such data may occur.

During hearings before the House Judiciary Committee on legislation that lead to enactment of the Biologics Act, representatives of BIO abjured reference to proposed legislative language as providing “marketing exclusivity” or “monopoly protection,” comparing the proposed language to the Hatch-Waxman Act provisions for data exclusivity and defining “data exclusivity” as the “period of time after the approval of the innovator’s product during which the FDA is not allowed to rely on the approval of the innovator’s product, including data contained in the [BLA], to support approval of the biosimilar product.”<sup>18</sup> It was commentary of this kind that lead Congressional actors to conclude that the Act “does not provide ‘market exclusivity’ for innovator products.”<sup>19</sup> Those representatives have recently emphasized these conclusions, stating to the FDA that the Act “provides *data* exclusivity for 12 years from the date of FDA approval (Title VII, Sec. 7002(7)(A)).” They added that there “are significant and critical differences between the two types of Exclusivity,” because “[d]ata exclusivity only prohibits the FDA from allowing another manufacturer to rely on the data of an innovator to support approval of another product,” but is “does not prohibit or prevent another manufacturer from developing its own data to justify FDA approval of a similar of competitive product.”<sup>20</sup> In contrast, “marketing exclusivity” would have provided a statutory monopoly, preventing a second manufacturer from obtaining approval of a “biosimilar” or “interchangeable” product, even based solely on its own data. No such “marketing exclusivity” is set forth in the Biologics Act, and the only statutory monopoly to which an initial reference product sponsor might be entitled is that conferred by any applicable patents.

*The November 2010 FDA Hearing: Statements About Exclusivity*

At the hearing on November 2 and 3, 2010, conducted pursuant to the Notice, a number of speakers addressed the issue framed by the FDA concerning eligibility for a “second 12-year period of marketing exclusivity.” Although the comments of those speakers were framed in scientific terms, the predicate for their comments was their understanding of the language and purpose of the Biologics Act. Some of those comments heighten levels of concern that the language of the Biologics Act may be misinterpreted and used to lengthen product lifecycles beyond those warranted by any real need to recover costs of investment in real innovation.

Several hearing speakers argued that “the statute provides that innovative products are entitled to exclusivity if they reflect *any* structural modification resulting in *any* change in the product’s safety, purity, or potency,” and that this “approach applies to all structural modifications without qualification.”<sup>21</sup> Under this extreme view of the Biologics Act, even small changes in structure of a biologics product would authorize the filing of an application by a reference product sponsor for a *new* 12-year period of exclusivity. While others were less demanding, the hearing left uncertainty about the manner in which the Biologics Act 12-year exclusivity provisions may be interpreted.

Some guidance may be obtained from remarks that were made about the broader Biologics Act question framed by the FDA: what factors should the agency consider in determining whether the biological product is highly similar to the reference product? Answers to this question are useful because the statutory definition of “biosimilar,” which refers to the safety, purity, and potency of the reference product, and the statutory prohibition on new periods of data exclusivity, which refers to modifications which result in a change in safety, purity, or potency, seem to rely upon similar conceptual foundations.

*The November 2010 FDA Hearing: Statements About Biosimilarity*

Some speakers at the FDA Hearing apparently interpreted the Biologics Act as permitting or requiring the FDA to mandate clinical studies and production of other scientific evidence by a follow-on biologics manufacturer that would render nearly meaningless the mandate for rapid approval of less expensive biologic equivalents. For example, one or more speakers argued that side-by-side clinical testing should be required for every indication for which a follow-on manufacturer seeks approval of an interchangeable or biosimilar biologic product. Such speakers argued that stringent requirements should be imposed for demonstration of structural and conformational similarity, exacting proof that biosimilar products must be shown to have the same amino acid sequence, the same or “highly similar” secondary and

tertiary structures. They stated that there must be “no divergence in safety or efficacy profiles.”<sup>22</sup>

Some speakers also suggested that the statutory language is unclear and that the FDA should not interpret the law in a manner that may allow a biosimilar to “evade the rights granted to an innovator.”<sup>23</sup> Others argued that, in order to protect the “rights granted to an innovator,” the FDA should interpret the Biologics Act to characterize a “modification to the structure, including but not limited to, the amino acid sequence,” or “critical post-translational features of the active ingredient,” or “changes in the biologic components,” as “resulting in a product with a change in safety, purity or potency as compared to the reference product.”<sup>24</sup>

The combined effect of these suggestions would interpret one portion of the Biologics Act, relating to biosimilarity or interchangeability, as permitting approval only on a showing of near identity to a reference product, while, at the same time, interpreting another portion of the statute to allow approval of a “new” version of the reference product, made by the “innovator,” with a showing of a relatively small change in the reference product. In short, these suggestions argue that minor differences in biologic products should result in denial of approval of competitive follow-ons, but that small structural and similar changes should be sufficient to justify granting a “new” period of data exclusivity to an innovator, which sponsored the reference product.

None of the speakers offered any statutory exegesis to support their positions. No such statutory analysis was explicitly required by the FDA’s public hearing notice. Nevertheless, the scientific and technical rationales offered by many speakers for their positions each depend implicitly on a particular understanding of the Biologics Act. The determination of the nature and quantity of proof may be required by the FDA to demonstrate that a biologic product is “highly similar ... notwithstanding minor differences in clinically inactive components,” is not only a scientific question; it must involve consideration of the intention of Congress when enacting the Biologics Act.

### *Analysis of the Biologics Act*

As noted above, the Biologics Act provides data exclusivity for a reference product, in much the same manner employed in the Hatch-Waxman Act, until the date that is 12 years after the date on which the reference product was first licensed.<sup>25</sup> The Biologics Act also prohibits the FDA from receiving a follow-on application until the date that is 4 years after the date on which the reference product was first licensed.<sup>26</sup>

The Biologics Act provides that the 12-year period of data exclusivity, and the 4-year stay of any follow-on application, will *not* apply to a license for or approval of—

- (i) a supplement for the biological product that is the reference product; or
- (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.*<sup>27</sup>

The language of the statute thus provides that the 12-year period of data exclusivity and the 4-year stay “shall not apply” in the circumstances set forth above. The language of the statute does *not* provide that, in the opposite case, where those circumstances are *not* present, that the FDA *must* recognize such exclusivity. Instead, the statutory language, at most, *permits* recognition of such exclusivity where the statutorily prescribed circumstances are *not* present, that is, where the FDA, in its discretion, finds that a modification to the structure of reference product results in “a change in safety, purity, or potency.”

The FDA Hearing speakers who argued that innovative products are entitled to exclusivity if they reflect *any* structural modification resulting in *any* change in the product’s safety, purity, or potency, read the statute obversely. They incorrectly read the statute to *require* the FDA to apply the 12-year period of data exclusivity and the 4-year stay of any follow-on application to approval of a subsequent application by the sponsor of the reference product for *any* modification to the structure of that product that results in a change in safety, purity, or potency. However, no *mandate* for affirmative recognition of exclusivity can be read from the statutory prohibition of such recognition in the statutorily prescribed circumstances.

The literal language of the statute, set forth above, contradicts the arguments made by such speakers. The final quoted phrase of the statute limits the potential grant of “new” data exclusivity to structural modifications to a reference product that “result in a change in

safety, purity, or potency.” That phrase does not state that “*any* change in safety, purity, or potency” of the reference product that might result from a structural modification is cognizable. The absence of this modifier (“any”) suggests that Congress meant something else. What else may be required can be discerned from other provisions in the Act, and from parts of its legislative history.

### *Biosimilarity*

The definition of “biosimilarity,” set forth elsewhere in the Biologics Act, provides some evidence of Congressional intent, and suggests that Congress did *not* intend to *require* that a *new* period of data exclusivity be recognized for *any* structural modification to a reference that results in *any* change in the product’s safety, purity, or potency “without qualification.” The term “biosimilar” is defined by the Biologics Act to mean

- (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, and potency of the product.*<sup>28</sup>

To be regarded as “biosimilar” or “interchangeable” under the Biologics Act, it must be shown to the satisfaction of the FDA that there are “*no* meaningful clinical differences” in safety, purity and potency between a follow-on product and the reference sponsor. In contrast, the Biologics Act prohibits successive grants of data exclusivity for a reference product, or a “new” grant of data exclusivity, unless it is shown that there *are* differences with respect to the safety, purity, and potency in a structurally modified reference product. Differences in the quantum and nature of scientific evidence may result from these statutory differences. In one case, the Biologics Act requires proof that there *are* differences; in the other, the Act requires proof that there are *no* meaningful clinical differences. Differences in the quantum and nature of required scientific evidence may also result from the differences in policy underlying these statutory provisions. The Congress clearly intended to define a “biosimilar” to enable the FDA to license follow-on biologic products. It also intended to prohibit successive grants of data exclusivity for a reference product. At minimum, such differences in statutory language and policy compel a conclusion that the scientific evidence required for any “new” period of data exclusivity must be far greater than that required to demonstrate “biosimilarity.”

The final phrase in the statutory definition of “biosimilar,” as noted above, refers to “the safety, purity, and potency of the [reference] product.” The use of the same words in the statutory prohibition on new periods of data exclusivity, quoted above, suggests that Congress meant for the two provisions to be interpreted in a similar manner. The inclusion of the words “*no clinically meaningful differences*” in the definition of “biosimilarity” demonstrates that Congress may have meant this standard to guide the FDA in all cases in which the similarity of *any* product to the reference product is considered. Hence, although these specific words are not included in the data exclusivity language of Biologics Act, their inclusion in the definition of “biosimilarity” strongly suggests that Congress meant for the FDA to grant a “new” period of data exclusivity only when a structural modification results in a change in safety, purity, or potency that is “clinically meaningful.”

This reading of the statute is also supported by the requirement that “biosimilar” products “shall be considered to have a new active ingredient,” while, at the same time, requiring that an “interchangeable” product “shall *not* be considered have a new active ingredient.”<sup>29</sup> Those products that are “highly similar” to the reference product, but have “minor differences in clinically inactive components” and “no clinically meaningful differences ... in terms of the safety, purity, and potency of the product,” when compared to the reference product, are “biosimilar” and are “considered to have a new active ingredient.” On the other hand, when all of these requirements are met and the follow-on product “may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product,” the follow-on product is “interchangeable,” and it is “*not* ... considered to have a new active ingredient.”

Likewise, if a structural modification to a reference product does not produce “clinically meaningful” differences in “safety, purity, or potency,” it is interchangeable with the reference product; it should “*not* be considered to have a new active ingredient;” and it should *not* be granted a “new” period of data exclusivity. At most, only structural modifications to a reference product that are scientifically shown to produce “clinically meaningful” differences in “safety, purity, or potency” warrant consideration of a structurally modified product as a “new active ingredient” that may be eligible for a “new” period of data exclusivity. As in other cases, the FDA has some discretion to make scientific and clinical judgments about the degree of “similarity” between a reference product and a structurally modified reference product.<sup>30</sup>

Hence, the Biologics Act requires proof of clinically meaningful differences in “safety, purity, or potency” by a reference product sponsor before the FDA *may* find that a structurally modified reference product should be regarded as a “new active ingredient” and granted a “new” period of data exclusivity.

### *Legislative History*

This construction of the language of the statute is consistent with the scant evidence of Congressional intent that may be inferred from the record of hearings and debate in the Congress. Perhaps most significant is the record of hearings before the House Judiciary Committee during the 111<sup>th</sup> Congress.<sup>31</sup> During those hearings, representatives of BIO testified and provided written submissions that related primarily to the appropriate period of data exclusivity that should be granted under the proposed legislation. Such data exclusivity, BIO argued, is necessary to preserve “the incentives that exist today in our vibrantly competitive and innovative biotechnology industry.” By the time of that testimony, BIO said, the only differences among the stakeholders and Congressional advocates revolved “around how long the data exclusivity period should be and how it should relate to continued clinical development of products.”<sup>32</sup> BIO argued for a data exclusivity period of 12 to 14 years.<sup>33</sup>

In a letter submitted along with its Prepared Statement to the House of Representatives, BIO acknowledged that “even when [reference product manufacturers] make changes in their *own* manufacturing processes, unanticipated changes in the product can and have occurred.”<sup>34</sup> The implication of these comments is that such “unanticipated changes” were not necessarily desirable, even if “clinically meaningful.” It was only for “second generation products” that BIO said “must go through the same rigorous FDA approval process as a first generation product,” including “development and submission of full clinical safety and efficacy data to support FDA review and approval of the complete marketing application [BLA or NDA],” that BIO asserted that “full data exclusivity” should be awarded.<sup>35</sup>

BIO’s remarks make clear that the language of Biologics Act, which generally prohibits the FDA from granting a “second” period of data exclusivity for structural modification of a reference product, should be read to permit the FDA to approve a “new” period of data exclusivity *only* for a “second generation” reference product. BIO’s remarks to Congress, unlike some of the remarks at the recent FDA hearing, support the conclusion that any “new” exclusivity that might be permitted under the Act must be narrowly limited to instances in which a “submission of full clinical safety and efficacy data to support FDA

review and approval of the complete marketing application," sufficiently demonstrates that "clinically meaningful" and patient favorable differences in "safety, purity, or potency" exist in a "second generation" product when compared to a reference product. Only such cases *might* warrant a finding by the FDA that a structurally modified product should be regarded as a "new active ingredient" for which a "new" period of exclusivity *might* be awarded. Absent "submission of full clinical safety and efficacy data to support" those findings, the Biologics Act requires that a structurally modified reference product should *not* be awarded any additional data exclusivity.

### *Conclusion*

In sum, the FDA should only consider a modification to the structure of the licensed reference biological product to warrant potential eligibility for a "new" 12-year period of data exclusivity, under the Biologics Act, if it is demonstrated in a "submission of full clinical safety and efficacy data to support FDA review and approval of the complete marketing application," that "clinically meaningful" and patient favorable differences in "safety, purity, or potency" exist in a "second generation" product when compared to a reference product. The FDA should otherwise obey the statutory prohibition of successive grants of periods of data exclusivity and it should deny any "new" period of data exclusivity when an application relating to a structurally modified reference product does not demonstrate, through "full clinical safety and efficacy data" that differences in "safety, purity, or potency" exist in a "second generation" product that are both "clinically meaningful" and patient favorable.

Any different interpretation will defeat one of the legislative purposes in creating a statutory basis for approval of biosimilar and interchangeable biologic products, to provide timely access to affordable biologic medicines and reduce our national health care expenditures. Any different interpretation will lead to evergreening practices entirely inconsistent with the intention of Congress in enacting the Biologics Act, and will defeat one of the Congressional purposes embodied in the Act: to bring competitive, biosimilar or interchangeable biologic products to consumers at lower cost, as quickly as possible.

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<sup>1</sup> J.M. Mueller & D.S. Chisum, *Enabling Patent Law's Inherent Anticipation Doctrine*, 45 Houston L. Rev. 1101, 1106 (2008). See also Congressional Research Service, 'Patent 'Evergreening': Issues in Innovation and Competition' at 1, 3 (2009), [http://www.ipmall.info/hosted\\_resources/crs/R40917\\_091113.pdf](http://www.ipmall.info/hosted_resources/crs/R40917_091113.pdf) (accessed January 19, 2011).

<sup>2</sup> M.E. Furrow, *Pharmaceutical Life Cycle Management After KSR v. Teleflex*, 63 Food and Drug L.J. 275, 298 (2008).

<sup>3</sup> Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Hatch-Waxman Act), Pub. L. No. 98-417, 98 Stat. 1585 (1984), codified at 21 U.S.C. §§ 355j, as amended by the Medicare Prescription Drug Improvement and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003) (collectively, the "Hatch-Waxman Act").

<sup>4</sup> See, e.g., Letter from Sen. Orrin Hatch et al. to FDA Commissioner Margaret Hamburg, dated January 7, 2011, <http://www.hpm.com/pdf/1-7-11%20Senate%20Biologics%20letter%20to%20FDA.pdf> (last accessed March 10, 2011); Letter from Rep. Anna Eshoo et al. to FDA Division of Dockets Management, dated December 21, 2010, <http://www.hpm.com/pdf/EIB%20Ltr%20FDA%20DEC%202010.pdf> (last accessed March 10, 2011); Letter from <http://www.hpm.com/pdf/1-24-11%20BPCIA%20Excl%20Letter%20to%20Hamburg.pdf> (last accessed March 10, 2011) (all letters from sponsors of the Biologics Act or others actively involved in debates over the Act, stating that Congress took concerns about "evergreening" seriously, adding that the legislation clearly provides "that no product, under any circumstances, can be granted 'bonus' years of data exclusivity for mere improvements on a product.")

<sup>5</sup> The Biologics Act also allows issuance of guidance by the FDA "that the science and experience, as of the date of such guidance, with respect to a product or product class (not including any recombinant protein) does not allow approval of an application for a license ...for such product or product class." The Act also makes clear that, except in cases where a guidance states that science does not allow approval, the "issuance (or non-issuance) of guidance under ... shall not preclude the review of, or action on, an application submitted under [the new Biologics Act]." *Id.*, § 7002(a), adding 42 U.S.C. § 262(k)(8). The failure of the FDA to issue guidance, like that already issued by the EMEA, is not a reason, therefore, for any delay in considering and acting on a "biosimilar" or "interchangeable" product application. See FDA Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing; Request for Comments, (2010) 75 Fed. Reg. 61497, <http://edocket.access.gpo.gov/2010/pdf/2010-24853.pdf> accessed 27 October 2010.

<sup>6</sup> *Id.*, § 7002(b), amending 42 U.S.C. § 262(i)(4)(defining "reference product").

<sup>7</sup> See 75 Fed. Reg. 61497 – 61501 (October 5, 2010).

<sup>8</sup> *Id.*, at 61497.

<sup>9</sup> See Notice, Topic G.2, 75 Fed. Reg. 61499 (emphasis added).

<sup>10</sup> Biologics Act, § 7002(a)(2), amending 42 U.S.C. §262 to add new §262 (k)(7)(A).

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<sup>11</sup> *Id.*, new §262 (k)(7)(B).

<sup>12</sup> See 21 U.S.C. §§ 262(c)(3)(E)(ii) and 262(j)(5)(F)(ii).

<sup>13</sup> See Biologics Act, § 7001(a)(2), amending 42 U.S.C. §262 to add new §262 (k)(7)(B). The Biologics Act defines a “reference product” as “the single biological product licensed under [the Biologics Control Act, 42 U.S.C. §262(a)], against which a biological product is evaluated in an application submitted under [the new Biologics Act].”

The Biologics Act requires an application for approval of a follow-on biologic product to include data demonstrating “biosimilarity” to a reference product based upon “analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components.” The application must include data from “animal studies (including the assessment of toxicity),” and from “a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product.” Biologics Act § 7002(a)(2), adding new §262(k)(2)(A)(i)(I)(aa – cc).

The Act also requires submission of data to demonstrate that “the biological product and reference product utilize the same mechanism or mechanisms of action,” if known; that “the condition or conditions of use prescribed ... in the [proposed] labeling ... have been previously approved for the reference product;” that “the route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product;” and that “the facility in which the biological product is manufactured ... meets standards designed to assure that the biological product continues to be safe, pure, and potent.” *Id.*, adding new §262(k)(2)(A)(i)(II - IV). The Act also requires follow-on product applications to include “publicly-available information regarding the Secretary’s previous determination that the reference product is safe, pure, and potent.” Such applications “may include any additional information in support of the application, including publicly available information with respect to the reference product or another biological product.” *Id.*, adding new §262(k)(2)(A)(iii). Compare Hatch Waxman Act, 21 U.S.C. §355(j)(2)(A).

<sup>14</sup> Biologics Act, § 7001(a)(2), amending 42 U.S.C. §262 to add new §262 (k)(2)(A)(i – iii). The Biologics Act permits the FDA to determine, in its discretion in a particular case or for a class of products, that such animal and clinical studies are unnecessary for approval of a “biosimilar” or “interchangeable” product. Biologics Act § 7002(a)(2), adding 42 U.S.C. §262(k)(2)(A)(ii).

<sup>15</sup> See Biologics Act, § 7001(a)(2), amending 42 U.S.C. §262 to add new §262 (k)(7)(A). The Hatch-Waxman Act, of course, has a similar 4 year initial period, but provides that the FDA may finally approve an ANDA 5 years (not 12) after first approval for marketing of a new chemical entity (NCE), subject to delay pending completion of patent litigation. See 21 U.S.C. § 355(j)(5)(F)(ii).

<sup>16</sup> See 21 U.S.C. §355(j)(4).

<sup>17</sup> Biologics Act § 7002(a)(2), adding new §262(k)(3).

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<sup>18</sup> See BIO Prepared Statement, in *Biologics and Biosimilars: Balancing Incentives for Innovation*, Hearing before the Subcommittee on Courts and Competition Policy of the House Judiciary Committee, Serial No. 111-73, 111<sup>th</sup> Cong, 1<sup>st</sup> Sess. (July 14, 2009) (“Biosimilar Hearings”), at 50 – 51. Compare H.R. 1548 (Pathway for Biosimilar Act), § 2 (amending Section 351 of the Public Health Service Act (42 U.S.C. 262), to add a new §351(k)(7)(A)) with Biologics Act, §262 (k)(7)(A).

<sup>19</sup> See Letter from Sen. Orrin Hatch, and Letter from Rep. Anna Eshoo, *supra*, Note 7.

<sup>20</sup> *Id.*

<sup>21</sup> The written remarks of that speaker continued: “This approach applies to all structural modifications without qualification. It thus applies to changes to the amino acid sequence, pegylation, and glycosylation, among other changes. It also applies to *all* changes in safety, purity, or potency, *without qualification*. The statute does not permit, for example, an inquiry into clinical superiority.” (emphasis supplied). See Novo Nordisk Testimony, at 5, <http://www.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480b811f7> (last visited December 6, 2010).

<sup>22</sup> Others stated that there should be no “second” period of marketing exclusivity for any biologic, “under any circumstances,” but they intimated or suggested that a “new” period of exclusivity would be appropriate under some circumstances. Compare FDA Hearing Slides, No. 24, at <http://www.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480b811e3> (last visited December 6, 2010) with Hearing Transcript, November 3, 2010, at 347.

<sup>23</sup> See FDA Hearing Transcript, November 3, 2010, at 350.

<sup>24</sup> See Bio Hearing Slides, No. 25, *supra*.

<sup>25</sup> Biologics Act, § 7002(a)(2), amending 42 U.S.C. §262 to add new §262 (k)(7)(A).

<sup>26</sup> *Id.*, §262(k)(7)(B).

<sup>27</sup> *Id.*, §262(k)(7)(C).

<sup>28</sup> Biologics Act, adding new §262(i)(2).

<sup>29</sup> Biologics Act, §7002(d), amending 21 U.S.C. §355(c) to add new subsections (n)(1) and (2).

<sup>30</sup> See *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313, 1320 (DC Cir. 1998) (FDA can make scientific judgments about “sameness”).

<sup>31</sup> See Biosimilar Hearings, *supra*, Note 16.

<sup>32</sup> See Testimony of Jeffrey Kushan, on behalf of the Biotechnology Industry Organization (BIO), in Biosimilar Hearings, *supra*, Note 16, at 38.

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<sup>33</sup> See also BIO Prepared Statement, *id.*, 40, 46, 50 – 56.

<sup>34</sup> See Letter dated September 30, 2008 from BIO to Federal Trade Commission, in Biosimilar Hearings, at 87, 90.

<sup>35</sup> *Id.*, at 95 – 96.

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