

## **Informed by the European Union Experience: What the United States Can Anticipate and Learn from the European Union’s Regulatory Approach to Biosimilars**

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## I. INTRODUCTION

Recombinant DNA technology has enabled the development of a variety of biopharmaceuticals, also known as biological products or biologics.<sup>1</sup> These products, which are made by or derived from living organisms using biotechnology, include erythropoietin, granulocyte colony-stimulating factors, human growth hormone, interferons, and vaccines, among others.<sup>2</sup> In both the United States and the European Union (EU), the patents for many biologics have recently expired or will soon do so. Thus, pharmaceutical firms in both regions currently focus on developing alternative versions of biologic products,<sup>3</sup> referred to as biosimilars, follow-on biologics, or follow-on protein products.<sup>4</sup>

Unlike traditional chemical pharmaceuticals, for which precise generic versions can be produced, biologics are inherently variable and cannot be manufactured as true generic equivalents.<sup>5</sup> Biologics have complex three-dimensional structures of high molecular weight, unlike traditional chemical drugs, which are of lower molecular weight and simpler in structure.<sup>6</sup> Consequently, current analytical techniques cannot characterize biologics with sufficient precision to confirm structural equivalence with reference molecules, meaning that biosimilars typically differ from their reference drug in ways that traditional chemical pharmaceuticals do not.<sup>7</sup>

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<sup>1</sup> See Håkan Mellstedt et al., *The Challenge of Biosimilars*, 19 ANNALS ONCOLOGY 411, 411 (2008).

<sup>2</sup> See *id.*; Steven Simoens, *Health Economics of Market Access for Biopharmaceuticals and Biosimilars*, 12 J. MED. ECON. 211, 212–13 (2009).

<sup>3</sup> See Mellstedt et al., *supra* note 1, at 411.

<sup>4</sup> See Donna M. Gitter, *Innovators and Imitators: An Analysis of Proposed Legislation Implementing an Abbreviated Approval Pathway for Follow-On Biologics in the United States*, 35 FLA. ST. U.L. REV. 555, 558 n.7 (2008) (noting that the term “follow-on biologic” refers to “proteins and peptides that are intended to be sufficiently similar to a product already approved under the Federal Food, Drug, and Cosmetic Act or licensed under the Public Health Service Act to permit the applicant to rely on certain existing scientific knowledge about the safety and effectiveness of the approved protein product” (citation omitted)); Huub Schellekens & Ellen Moors, *Clinical Comparability and European Biosimilar Regulations*, 28 NATURE BIOTECH. 28, 28 (2010) (noting that the EU typically uses the term “biosimilar”).

<sup>5</sup> See Mellstedt et al., *supra* note 1, at 412.

<sup>6</sup> See JUDITH A. JOHNSON, CONG. RESEARCH SERV., FDA REGULATION OF FOLLOW-ON BIOLOGICS 9 (Apr. 26, 2010), available at [http://www.primaryimmune.org/advocacy\\_center/pdfs/health\\_care\\_reform/Biosimilars\\_Congressional\\_Research\\_Service\\_Report.pdf](http://www.primaryimmune.org/advocacy_center/pdfs/health_care_reform/Biosimilars_Congressional_Research_Service_Report.pdf); see also Simoens, *supra* note 2, at 211.

<sup>7</sup> See Huub Schellekens, *Biosimilar Therapeutics—What Do We Need to Consider?*, 2 NEPHROLOGY DIALYSIS TRANSPLANTATION PLUS (SUPP. 1) i27, i27 (2009); see also Gitter, *supra* note 4, at 560–61; Simoens, *supra* note 2, at 212–13 (describing the differences

The complexity and heterogeneity of biologics derive largely from the manufacturing processes used to produce them. Biologics are made within living cells, and minute changes in the process can result in differences in quality, safety, and efficacy.<sup>8</sup> Thus, biologics differ within a single batch, from one batch to another made by the same company, and among companies producing the same biologic.<sup>9</sup> In contrast, traditional chemical drugs are synthesized using a predictable process that creates identical versions of the innovator drug.<sup>10</sup>

The inherent unpredictability of biologics, whether they are innovator or follow-on products, also arises from the fact that biologics raise issues of immunogenicity. Unlike traditional chemical pharmaceutical products, most biologics stimulate an immune response in the human body, prompting the formation of antibodies that may affect human health.<sup>11</sup>

Thus, due to their complex structures, sensitivity to the manufacturing process, and tendency toward immunogenicity, biosimilars cannot be considered generic biopharmaceuticals, but rather new, non-innovative products that are similar, but not identical, to a reference biopharmaceutical product in terms of efficacy and safety.<sup>12</sup>

Notwithstanding the challenges in manufacturing biosimilars, the EU successfully implemented an abbreviated approval pathway for follow-on biologics in 2005.<sup>13</sup> An abbreviated approval pathway for biologics permits a pharmaceutical company applying for regulatory approval to rely, to at least some extent, on the regulatory authority's conclusions regarding the quality, safety, and efficacy of an approved reference product.<sup>14</sup> In this way, the manufacturer of the follow-on product avoids some, though not necessarily all, of the cost-

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between biologics and traditional chemical pharmaceuticals, which render the former more complex, difficult to characterize, and harder to manufacture than the latter).

<sup>8</sup> See Schellekens, *supra* note 7, at i27–i28.

<sup>9</sup> See Gitter, *supra* note 4, at 561; Schellekens, *supra* note 7, at i27–i28. Moreover, biosimilar manufacturers do not have access to the manufacturing processes of innovator products because this information is proprietary, rendering precise replication of the reference product impossible. Mellstedt et al., *supra* note 1, at 412.

<sup>10</sup> See Simoens, *supra* note 2, at 211.

<sup>11</sup> See Gitter, *supra* note 4, at 561; Schellekens, *supra* note 7, at i29.

<sup>12</sup> See Mellstedt et al., *supra* note 1, at 411, 415.

<sup>13</sup> See Meredith Waldman, *U.S. Health Bill Promises Changes for Biomedical Researchers*, 464 NATURE 479, 479 (2010).

<sup>14</sup> See Schellekens, *supra* note 7, at i31.

ly pre-clinical and clinical testing<sup>15</sup> necessary for regulatory approval.<sup>16</sup> As of this writing, the European Medicines Agency (EMA), the European equivalent of the U.S. Food and Drug Administration (FDA),<sup>17</sup> has granted marketing authorization to fourteen biosimilar products.<sup>18</sup>

In the United States, the Hatch-Waxman Act (HWA) has provided an abbreviated approval pathway for traditional chemical pharmaceuticals since 1984.<sup>19</sup> For these pharmaceuticals, it is relatively easy to demonstrate that a generic product is equivalent to the reference drug. Experts have noted that “[a]ll that is required is proof that the generic product contains the identical chemical composition as the innovator product and a bioavailability study showing that the pharmacokinetic properties of the generic and reference products are similar.”<sup>20</sup>

After years of debate in the United States regarding an abbreviated approval pathway for follow-on biologics analogous to the HWA for traditional pharmaceuticals,<sup>21</sup> on March 23, 2010, President

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<sup>15</sup> Pre-clinical trials, sometimes called non-clinical trials, test a pharmaceutical product in a lab or on animals, while clinical trials test the drug in humans. RACHEL CHU & MEIR PUGATCH, STOCKHOLM NETWORK, BIOGENERIC OR BIOSIMILARS? DISCUSSING THE PRESENT, CONSIDERING THE FUTURE 9 n.9 (2009), available at [http://www.stockholm-network.org/downloads/publications/Biosimilars\\_final.pdf](http://www.stockholm-network.org/downloads/publications/Biosimilars_final.pdf).

<sup>16</sup> See Schellekens, *supra* note 7, at i31. “The amount of data required for market approval of biosimilars will be more than for a typical generic drug application but less than for a full new biopharmaceutical application.” *Id.*

<sup>17</sup> Brian A. Liang, *Regulating Follow-on Biologics*, 44 HARV. J. ON LEGIS. 363, 397 (2007). The EMA, which was reorganized in 2009, was formerly known by the acronym EMEA. *EMEA Becomes EMA*, PMLIVE INTELLIGENCE ONLINE (Dec. 14, 2009), [http://www.pmlive.com/find\\_an\\_article/allarticles/categories/General/2009/december/news/emea\\_becomes\\_ema](http://www.pmlive.com/find_an_article/allarticles/categories/General/2009/december/news/emea_becomes_ema).

<sup>18</sup> E-mail from Anna Nagielska, Document and Information Services, European Medicines Agency, to author (July 23, 2010, 06:47 EST) (on file with author).

<sup>19</sup> Pub. L. No. 98-417, 98 Stat. 1585 (1984) (amending the Federal Food, Drug, and Cosmetic Act Pub. L. 75-717, § 505(j), 52 Stat. 1040 (1938), codified at 21 U.S.C. § 355(j) (2010)).

<sup>20</sup> Mellstedt et al., *supra* note 1, at 412 (citation omitted). Pharmacokinetics is described as “what the body does to a drug” and “refers to the movement of drug into, through, and out of the body—the time course of its absorption, bioavailability, distribution, metabolism, and excretion.” *Clinical Pharmacology, Pharmacokinetics, Introduction*, THE MERCK MANUALS, <http://www.merck.com/mmpe/sec20/ch303/ch303a.html> (last visited Mar. 1, 2011).

<sup>21</sup> See KEITH J. HARRISON, BIOSIMILARS INDIA 2009: MAPPING OUT THE LATEST DEVELOPMENTS IN EUROPEAN AND U.S. BIOSIMILAR REGULATION—ACHIEVING COST-EFFECTIVE COMPLIANCE 16–18 (Dec. 2, 2009), available at <http://www.crowell.com/documents/Mapping-Out-Latest-Developments-European-And%20US%20Biosimilar%20Regulation-Achieving-Cost-Effective-Compliance.pdf>

Barack Obama signed into law the Biologics Price Competition and Innovation Act of 2009 (BPCIA).<sup>22</sup> The BPCIA forms part of the much-debated health care reform bill known as the Patient Protection and Affordable Care Act.<sup>23</sup> With the enactment of the BPCIA, manufacturers of follow-on biologics will be able to file abbreviated applications for FDA approval for follow-on biologics.<sup>24</sup> With this legislation, Congress seeks to provide sufficient protection for innovator firms that have created biological products while simultaneously fostering robust competition from follow-on competitors.<sup>25</sup> Follow-on biologic applicants will aim to ensure that their products meet the FDA's criteria for biosimilarity to the corresponding reference products yet remain different enough, either in composition or method of manufacture, so as to avoid infringing any of the patents covering the reference products. According to the Congressional Budget Office, the legislation is expected to save the federal government approximately \$7 billion over the next decade in drug costs.<sup>26</sup>

Most of the policy debate surrounding the BPCIA concerned the appropriate period, if any, of data exclusivity, meaning the period of time that an innovator firm's pre-clinical and clinical data cannot be

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(outlining the protracted debate in the United States regarding the development of an abbreviated approval pathway for follow-on biologics).

<sup>22</sup> Patient Protection and Affordable Care Act, Pub. L. No. 111-148, §§ 7001-03, 124 Stat. 119, 804-21 (2010) [hereinafter BPCIA]; Nathan Beaver et al., *Update—United States Enacts Approval Pathway for Biosimilars*, MONDAQ BUSINESS BRIEFING, Apr. 15, 2010.

<sup>23</sup> Patient Protection and Affordable Care Act, Pub. L. No. 111-148, 124 Stat. 119 (2010) (codified in scattered sections of 21 U.S.C., 35 U.S.C., and 42 U.S.C.).

<sup>24</sup> The FDA defines an abbreviated application as "one that relies, to at least some extent, on the Agency's conclusions regarding the safety and effectiveness (or safety, purity, and potency) of an approved product and also contains additional data necessary, other than the underlying clinical data supporting the approved product, to establish that the follow-on product is safe and effective." *Safe and Affordable Biotech Drugs—The Need for a Generic Pathway: Hearing Before the H. Comm. on Oversight and Government Reform*, 110th Cong. 5 (2007) (statement of Janet Woodcock, M.D., Deputy Commissioner, Chief Medical Officer, U.S. Food & Drug Admin.), available at <http://www.hhs.gov/asl/testify/2007/04/t20070326a.html>. The BPCIA defines the term "biological product," also known as a biologic or biopharmaceutical, as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings." BPCIA § 7002(b)(1) (amending 42 U.S.C. § 262(i) (2006)).

<sup>25</sup> See Doug Trapp, *Health Reform Law Gives Biologic Drugs 12-Year Exclusivity*, AMEDNEWS.COM, Apr. 12, 2010, <http://www.ama-assn.org/amednews/2010/04/12/gvsa0412.htm>.

<sup>26</sup> *Id.*

used by a follow-on competitor.<sup>27</sup> This issue did not arise in the EU because manufacturers of innovative biologics enjoy the same exclusivity period as manufacturers of innovative chemical pharmaceuticals.<sup>28</sup> Now that it has enacted the BPCIA, the United States can look to the EU to determine the salient regulatory and policy issues that have come to the fore in that region during the last several years, after its enactment of an abbreviated approval pathway for biologics.

Currently, the EU is grappling with the following six questions: (1) how to assess comparability of the reference and follow-on biologic products; (2) whether to designate a biologic as interchangeable with the reference product; (3) the appropriate levels of immunogenicity testing, pharmacovigilance, and risk assessment for biosimilars; (4) the propriety of giving a follow-on biologic the same name as the reference product; (5) the approval of a biosimilar drug for indications for which it has not been evaluated in clinical trials, based on extrapolation of data from the reference product; and (6) potential extensions to the term of data exclusivity for biosimilars. This Article will consider how the EU is dealing with these challenges with a view toward applying these lessons to the United States. A full consideration of these questions requires an understanding of the recently enacted BPCIA, as well as the EU legislative approval pathway for biosimilars.

## II. THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009

### A. *The Follow-On Biologic Application and Approval Process Under the BPCIA*

The BPCIA provides that a follow-on biologic may be approved by the Secretary of the U.S. Department of Health and Human Services (“the Secretary”)<sup>29</sup> if it is “biosimilar” to the reference product.<sup>30</sup>

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<sup>27</sup> See e.g., *Safe and Affordable Biotech Drugs—The Need for a Generic Pathway: Hearing Before the H. Comm. on Oversight and Government Reform*, 110th Cong. 174–75 (2007) (statement of Henry G. Grabowski, Ph.D.), available at <http://docs.govdoc.org/us/legi/house/cogr/hearings/HHRG-110-0043.pdf> (testifying, during Congressional hearings regarding an earlier draft biologics bill, in favor of a data exclusivity period for innovator biologics of at least ten years, akin to that of the EU) [hereinafter Grabowski Testimony]; Gitter, *supra* note 4, at 613–16 (describing the debate among industry representatives, legislators, and academics regarding data exclusivity for innovator biologics and advocating for ten to twelve years of data exclusivity).

<sup>28</sup> See *infra* notes 42–45 and accompanying text.

<sup>29</sup> 42 U.S.C. § 262(k)(3) (Supp. IV 2010).

<sup>30</sup> § 262(k)(2)(A)(i)(I).

Biosimilarity is defined to mean “that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and “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>31</sup> To assess biosimilarity, the FDA will determine, among other things, whether: (1) the follow-on product is “highly similar” to the reference product based on data from analytical, animal, and clinical studies; (2) the two products have the same mechanism of action, to the extent such mechanism is known; and (3) the conditions of use in the labeling for the proposed biological product have been previously approved for the reference product; and (4) the route of administration, dosage form, and strength of the two products are the same.<sup>32</sup> The BPCIA also provides that the Secretary “may determine, in the Secretary’s discretion, that any of these elements [considered for a showing of biosimilarity] is unnecessary.”<sup>33</sup>

An applicant may also include in its application information demonstrating that its biological product meets a higher standard, namely, interchangeability.<sup>34</sup> For a follow-on biologic to be deemed interchangeable, the applicant must demonstrate that the biological product is biosimilar to the reference product and “can be expected to produce the same clinical result as the reference product in any given patient.”<sup>35</sup> Interchangeable products can then be substituted by a pharmacy without physician approval.<sup>36</sup> With the enactment of the BPCIA, the FDA will issue guidance, after the requisite notice and comment period, for follow-on firms seeking to achieve designations of biosimilarity and interchangeability.<sup>37</sup>

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<sup>31</sup> § 262(i)(2)(B).

<sup>32</sup> § 262(k)(2)(A)(i)(I)–(IV).

<sup>33</sup> § 262(k)(2)(A)(ii).

<sup>34</sup> § 262(k)(2)(B).

<sup>35</sup> 42 U.S.C. § 262(k)(2)(B)(4) (Supp. IV 2010). Furthermore, if a biological product “is administered more than once to an individual,” it will be deemed interchangeable only if “the risk in terms of safety and diminished efficacy of alternating or switching between the use of the biological and the reference product is not greater than the risk of using the reference product without such alternation or switch.” *Id.*

<sup>36</sup> § 262(i)(3).

<sup>37</sup> § 262(k)(8).

B. *Exclusivity Provisions for Reference Biologics Pursuant to the BPCIA*

The thorniest issue relating to the enactment of the BPCIA involved the length of the statutory exclusivity period for reference biologics. Pursuant to the HWA, which provides an abbreviated approval pathway for traditional chemical pharmaceuticals,<sup>38</sup> and upon which the BPCIA is modeled,<sup>39</sup> there are two types of exclusivity: market exclusivity and data exclusivity. Market exclusivity is defined as “a period of time during which the FDA affords an approved drug protection from competing applications for marketing approval.”<sup>40</sup> Under the HWA, the marketing exclusivity provision precludes the FDA from approving any abbreviated new drug application for a generic drug for five years from the date the FDA approved the corresponding reference drug, if that reference drug is a new chemical entity.<sup>41</sup>

While the terms market exclusivity and data exclusivity are often considered synonymous under the HWA,<sup>42</sup> in the EU these terms are usually parsed more precisely. Throughout the EU, all branded medicinal products, including traditional chemical pharmaceuticals and biologics, are governed by the 8+2+1 rule.<sup>43</sup> The innovator may receive up to eight years of data exclusivity, which means that a follow-on firm may not even submit a biosimilar application that relies on an innovator firm’s data until eight years after the EMA’s authorization

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<sup>38</sup> Pub. L. No. 98-417, 98 Stat. 1585 (1984) (amending the Federal Food, Drug, and Cosmetic Act Pub. L. 75-717, § 505(j), 52 Stat. 1040 (1938), codified at 21 U.S.C. § 355(j) (2006)). Under the HWA, generic drug manufacturers are typically not required to submit pre-clinical and clinical data along with their abbreviated new drug applications, thereby by-passing the significant expenses associated with developing new pharmaceuticals. *See id.* In order to take advantage of this abbreviated pathway, the generic manufacturer must prove that the generic version of the drug contains the same active ingredient as the original, demonstrates bioequivalence to the original, and is manufactured according to appropriate practices. *See* 21 U.S.C. § 355(j) (2) (A).

<sup>39</sup> *See* Ralph A. Loren & Thomas H. Wintner, *New Law! The Biologics Price Competition and Innovation Act of 2009*, MARTINDALE.COM (Apr. 12, 2010), [http://www.martindale.com/health-care-law/article\\_Edwards-Angell-Palmer-Dodge-LLP\\_976250.htm](http://www.martindale.com/health-care-law/article_Edwards-Angell-Palmer-Dodge-LLP_976250.htm).

<sup>40</sup> WENDY H. SCHACHT & JOHN R. THOMAS, CONG. RESEARCH SERV., RL 33901, FOLLOW-ON BIOLOGICS: INTELLECTUAL PROPERTY AND INNOVATION ISSUES 13 (2009), available at [http://www.ipmall.info/hosted\\_resources/crs/RL33901\\_090320.pdf](http://www.ipmall.info/hosted_resources/crs/RL33901_090320.pdf).

<sup>41</sup> 21 U.S.C. § 355(j)(5)(F)(ii) (2006); 21 C.F.R. § 314.108(b)(2) (2010). The period of market exclusivity is three years after the approval date if the innovator drug is not a new chemical entity. § 355(j)(5)(F)(iii).

<sup>42</sup> *See* Grabowski Testimony, *supra* note 27, at 172–74.

<sup>43</sup> *See* Joyce Wing Yan Tam, *Biologics Revolution: The Intersection of Biotechnology, Patent Law, and Pharmaceutical Regulation*, 98 GEO. L.J. 535, 554 (2010).



of the reference product.<sup>44</sup> What is more, the branded firm receives an additional two years of purely market exclusivity, meaning that the follow-on firm may not market the biosimilar product until ten years (i.e., 8 + 2) have elapsed from the EMA's authorization of the reference product.<sup>45</sup> In addition, the period of exclusivity can be extended to a maximum of eleven years (8 + 2 + 1) if, during the first eight years of data exclusivity, the holder of the reference product "obtains an authorisation for new therapeutic indication(s) which bring(s) significant clinical benefits in comparison with existing therapies."<sup>46</sup>

In discussions regarding the BPCIA, innovator firms, represented by the Biotechnology Industry Organization trade group, sought an exclusivity period totaling fourteen years, while the Generic Pharmaceutical Association sought much less.<sup>47</sup> Indeed, one draft version of the legislation provided for no market exclusivity period whatsoever for the reference drug.<sup>48</sup> Meanwhile, scholars and policy makers supported varying periods of exclusivity.<sup>49</sup>

The BPCIA ultimately established a four-year data exclusivity period to run concurrently with a twelve-year market exclusivity period for reference biologic drugs.<sup>50</sup> A follow-on biologic application may not be submitted until four years after the FDA's authorization of the reference product, and a follow-on biologic application may not be

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<sup>44</sup> See *id.*

<sup>45</sup> *Follow-On Biologics: Hearing Before the S. Comm. on Health, Education, Labor and Pensions*, 110th Cong. 3 (2007) (statement of Nicolas Rossignol, Administrator, European Commission, Pharmaceuticals Unit), available at <http://help.senate.gov/imo/media/doc/Rossignol.pdf> [hereinafter Rossignol Testimony]; see also Elisabeth Berthet-Maillols, *Biosimilar EPO: The Reasons to Be Confident*, 6 J. GENERIC MEDS. 111, 114 (2009).

<sup>46</sup> Rossignol Testimony, *supra* note 45, at 3.

<sup>47</sup> Trapp, *supra* note 25.

<sup>48</sup> See Gitter, *supra* note 4, at 611–12.

<sup>49</sup> See, e.g., Grabowski Testimony, *supra* note 27, at 174 ("A ten year exclusivity period, like that currently exists in Europe, would help balance innovation incentives and price competition when instituting a new regulatory pathway for biologicals."); David E. Adelman & Christopher M. Holman, *Misplaced Fears in the Legislative Battle Over Affordable Biotech Drugs*, 50 IDEA 565, 565–70 (2010) (favoring a twelve-year data exclusivity period for biologics); Gitter, *supra* note 4, at 613–16.

[A] data protection period of ten to twelve years, which would run concurrently with the patent term for the product, would provide pioneer firms with the assurance that they would earn a reasonable monopoly period in return for the time, money, and effort they expended in developing an innovator biologic product.

*Id.* at 616.

<sup>50</sup> 42 U.S.C. § 262(k)(7)(A)–(B) (Supp. IV 2010).

approved by the FDA until twelve years after FDA authorization of the reference product.<sup>51</sup> Thus, unlike the EU, which affords biologics the same data and marketing exclusivity periods as any other innovative drug,<sup>52</sup> the United States has established a separate exclusivity period for biologics.

C. *Patent Infringement Issues Relating to the BPCIA*

Another salient feature of the BPCIA, which is markedly different from the HWA, is the process by which a follow-on manufacturer can learn about the patents relating to the reference product. With respect to traditional chemical drugs, once the FDA approves a new product, the agency publishes the drug name and related patent information in its Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book.<sup>53</sup> The HWA includes this provision in order to provide the public, including generic manufacturers of traditional chemical drugs, with information about patents held by innovator firms.<sup>54</sup> Manufacturers of biologics, however, do not publish their patent information in the Orange Book.<sup>55</sup> In order to provide manufacturers of follow-on biologics with information about patents held by innovator firms, analogous to the information enjoyed by manufacturers of generic drugs, the BPCIA requires a process of information exchange between the reference product sponsor, typically the patent holder or licensee, and the follow-on biologic applicant.<sup>56</sup>

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<sup>51</sup> *Id.* In addition, an additional six months of exclusivity may be obtained for approved pediatric or rare disease indications. § 262(m). The BPCIA also provides exclusivity for the first interchangeable biological product. § 262(k)(6). In contrast, the EU does not afford any exclusivity to biosimilar products. See CHU & PUGATCH, *supra* note 15, at 22.

<sup>52</sup> See *supra* note 43 and accompanying text.

<sup>53</sup> See 21 C.F.R. § 314.3(b) (2010). The Approved Drug Products with Therapeutic Equivalence Evaluations is commonly referred to as the Orange Book. *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, U.S. FOOD & DRUG ADMIN. <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm> (last visited Jan. 29, 2011).

<sup>54</sup> See Cynthia H. Zhang, *Innovator vs. Generic: The Interplay of Patent Delisting and 180-Day Market Exclusivity*, 5 TRENDS IN BIO/PHARMACEUTICAL INDUSTRY 16, 17 (2009).

<sup>55</sup> Tam Q. Dinh, *Potential Pathways for Abbreviated Approval of Generic Biologics under Existing Law and Proposed Reforms to the Law*, 62 FOOD & DRUG L.J. 77, 111 (2007) (stating that “a biologic approved under a BLA is not listed in the *Orange Book*”).

<sup>56</sup> See Loren & Wintner, *supra* note 39. For the details of this process, see 42 U.S.C. § 262(l) (Supp. IV 2010).

## III. THE EUROPEAN UNION LEGISLATIVE FRAMEWORK FOR BIOSIMILARS

The EU legislative framework for abbreviated approval of biosimilars proves instructive in light of the similarities between EU and U.S. pharmaceutical approval processes. In both regions, all biotechnological products, including biosimilars, undergo rigorous review and a centralized approval process.<sup>57</sup> Moreover, both regions offer patent protection for twenty years from the filing of the application as well as a strong commitment to intellectual property rights and the implementation of an exclusivity period for firms that create new products.<sup>58</sup>

In 2005 the EU successfully established a comprehensive regulatory pathway for biosimilar products.<sup>59</sup> It was the first region in the world to do so.<sup>60</sup> Branded biologics must proceed through a centralized regulatory process, mediated by the EMA, which is effective throughout all twenty-seven EU Member States.<sup>61</sup> In contrast, traditional chemical pharmaceuticals may submit either to the centralized authorization process or, alternatively, to national authorization procedures.<sup>62</sup> In its role as the agency evaluating all biologics, the EMA and its scientific Committee for Medicinal Products for Human Use (CHMP)<sup>63</sup> developed several guidance documents to create detailed

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<sup>57</sup> See LINDA R. HORTON, THE EUROPEAN EXPERIENCE WITH FOLLOW-ON BIOLOGICS LEGISLATION 4 (2008), available at <http://www.ftc.gov/bc/workshops/hcbio/docs/fob/lhortonsv.pdf>.

<sup>58</sup> *Id.* It should also be noted that the U.S. and EU differ in some significant ways. For example, each of the twenty-seven EU Member States has its own health-care system and exercises self-determination with respect to pharmaceutical reimbursement, pricing, and substitutability. *Id.* Moreover, in the EU, national differences persist in the patent systems. *Id.*

<sup>59</sup> See Council Directive 2004/27, 2004 O.J. (L 136) 47, 34–57 (EC) (amending Directive 2001/83 on the Community Code Relating to Medicinal Products for Human Use); Commission Regulation 726/2004, 2004 O.J. (L 136) 1–33 (EC).

<sup>60</sup> See Schellekens & Moors, *supra* note 4, at 30.

<sup>61</sup> Central Authorisation of Medicines, EUR. MEDS. AGENCY [hereinafter EMA], [http://www.ema.europa.eu/ema/index.jsp?curl=pages/about\\_us/general/general\\_content\\_000109.jsp&murl=menus/about\\_us/about\\_us.jsp&mid=WC0b01ac0580028a47&jsenabled=true](http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028a47&jsenabled=true) (last visited Mar. 2, 2011); see also Simoens, *supra* note 2, at 213 (noting that the EMA assesses biopharmaceuticals through the centralized procedure).

<sup>62</sup> EMA, *supra* note 61.

<sup>63</sup> See Liang, *supra* note 17, at 398–99. For human drugs, once a company submits a marketing authorization application to the EMA as part of the centralized process, the CHMP, which is the scientific arm of the EMA, evaluates the product. *Id.* If the CHMP concludes that the product meets the requisite quality, safety, and efficacy standards, CHMP sends this recommendation to the European Commission, which may, in its discretion, issue a market authorization valid throughout the EU. *Id.* The

criteria for approval.<sup>64</sup> The three essential requirements of the EMA CHMP guidelines for biosimilars are (1) the provision of the requisite

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CHMP is also charged with some post-authorization responsibilities, such as review of modifications and extensions of the existing marketing authorization. *Id.*

<sup>64</sup> See Schellekens & Moors, *supra* note 4, at 28. The first EMA/CHMP guideline regarding biologics, the *Guideline on Similar Biological Medicinal Products*, which came into effect in October 2005, aimed “to introduce the concept of similar biological medicinal products; to outline the basic principles to be applied; and to provide applicants with a ‘user guide’, showing where to find relevant scientific information in the various CHMP guidelines in order to substantiate the claim of similarity.” Eur. Meds. Agency [EMA], *Guideline of Similar Biological Medicinal Products*, at 3, EMEA Doc. No. CHMP/437/04 (Oct. 30, 2005), available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003517.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf) [hereinafter EMA, EMEA/CHMP/437/04]. In June 2006, two additional EMA/CHMP guidelines came into effect. The *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Quality Issues* aims to establish “the quality requirements for a biological medicinal product claiming to be similar to another one already marketed.” EMA, *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Quality Issues*, at 3, EMEA Doc. No. CHMP/BWP/49348/2005 (Feb. 22, 2006), available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003953.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003953.pdf) [hereinafter EMA, EMEA/CHMP/49348/2005]. This document addresses requirements pertaining to biosimilars with respect to manufacturing processes, analytical methods to assess comparability, factors to consider when choosing a reference product, and physicochemical and biological characterization of biosimilars. *Id.* The *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues*, which also took effect in June 2006, addresses pre-clinical requirements for biosimilars, mainly pharmacotoxicological assessment, along with clinical requirements, namely, pharmacokinetic, pharmacodynamic, efficacy, and safety studies, with an emphasis on evaluating the immunogenicity of biosimilars. EMA, *Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues*, at 3, EMEA Doc. No. CHMP/BWP/42832/2005 (Feb. 22, 2006), available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003920.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003920.pdf) [hereinafter EMA, EMEA/CHMP/BWP/42832/2005]. In April 2008, the *Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins* came into effect. EMA, *Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins*, at 1, EMEA Doc. No. CHMP/BWP/14327/2006 (Dec. 13, 2007), available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003946.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003946.pdf). This document considers the immunogenic issues that biopharmaceutical companies must address for approval of a biosimilar product or when a manufacturing change occurs. *Id.* at 4. These include factors that affect immunogenicity and the potential consequences of it; the development, design, and interpretation of pre-clinical and clinical assays to evaluate the immunogenic potency of a product and its comparability to other products; and the implementation of a risk management plan. *See id.* at 7–13.

Finally, the EMA/CHMP has also adopted six product-specific guidelines, relating to the development of biosimilars containing recombinant erythropoietin; recombinant interferon alpha; low-molecular-weight-heparin; somatropin; human insulin; and granulocyte colony-stimulating factor. E-mail from Anna Nagielska, Document and Information Services, European Medicines Agency, to author (July 29, 2010, 10:13 EST) (on file with author). These documents set forth pre-clinical

pre-clinical and clinical data; (2) a comparability exercise to show biosimilarity in quality, efficacy, and safety; and (3) product-specific pharmacovigilance and risk management plans to monitor potential immunogenicity.<sup>65</sup>

With respect to the first requirement, the EMA's regulatory framework for biosimilars mandates clinical trial data in order to

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and clinical data requirements for marketing approval, describing the size of the clinical trials required and the best means of demonstrating equivalence for each product in comparison to the reference product. See EMA, *Guideline on Clinical and Non-Clinical Development of Similar Biological Medicinal Products Containing Recombinant Erythropoietins (Revision)*, at 3, EMEA Doc. No. CHMP/BMWP/301636/2008 (Mar. 18, 2010), available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2010/04/WC500089474.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/04/WC500089474.pdf) (Mar. 18, 2010) [hereinafter EMA, EMEA/CHMP/BMWP/301636/2008]; EMA, *Reflection Paper on Non-Clinical and Clinical Development of Similar Medicinal Products Containing Recombinant Interferon Alpha*, at 3, EMEA Doc. No. CHMP/BMWP/118264/07 (Apr. 23, 2009), available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003930.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003930.pdf) [hereinafter EMA, EMEA/CHMP/BMWP/301636/2008]; EMA, *Guideline on Clinical and Non-Clinical Development of Similar Biological Medicinal Products Containing Low-Molecular-Weight-Heparins*, at 3, EMEA Doc. No. CHMP/BMWP/118264/07 (Mar. 19, 2009), available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003927.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003927.pdf); EMA, *Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues: Guidance on Similar Medicinal Products Containing Somatropin*, at 3, EMEA Doc. No. CHMP/94528/2005 (Feb. 22, 2006), available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003956.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003956.pdf) [hereinafter EMA, EMEA/CHMP/94528/2005]; EMA, *Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues: Guidance on Similar Medicinal Products Containing Recombinant Human Soluble Insulin*, at 3, EMEA Doc. No. CHMP/32775/05 (Feb. 22, 2006), available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003957.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003957.pdf) [hereinafter EMA, EMEA/CHMP/32775/05]; EMA, *Annex to Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues: Guidance on Similar Medicinal Products Containing Recombinant Granulocyte-Colony Stimulating Factor*, at 3, EMEA Doc. No. CHMP/31329/2005 (Feb. 22, 2006), available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500003955.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003955.pdf) [hereinafter EMA, EMEA/CHMP/31329/2005].

<sup>65</sup> See Kadriye Ciftci, *Biosimilars or Follow-on Biologics: Scientific and Regulatory Considerations*, ICON INSIGHT, Mar. 2010, <http://www.iconplc.com/icon-files/insight-newsletter/Spring10/biosimilars.html> ("Regulatory authorities agree that non-clinical and clinical data are needed to demonstrate the safety and efficacy of a biosimilar. In addition, post-marketing surveillance and Risk Management Plans should be in place for the approval of biosimilar products." (citations omitted)); Schellekens, *supra* note 7, at i31 (describing the EMA's requirements for pre-clinical and clinical data; a comparability analysis; and pharmacovigilance plans); Schellekens & Moors, *supra* note 4, at 30 (noting the EMA's need for pre-clinical and clinical data and a comparability exercise in order to approve a biosimilar).

demonstrate that the follow-on products are effective and safe.<sup>66</sup> The EMA takes a case-by-case approach, acknowledging that while “the concept of ‘a similar biological medicinal product’ is theoretically applicable to any biological medicinal product,” in practical terms, the success of an abbreviated approval pathway for biosimilars “will depend on the ability to characterise the product and therefore to demonstrate the similar nature of the concerned products.”<sup>67</sup> The applicant “may not be required to repeat full safety and efficacy testing, but the EMA retains the discretion to require the full array of pre-clinical and clinical data if the biologic’s structure is too complex to establish equivalence adequately.”<sup>68</sup> For example, immunologicals, such as vaccines and allergens, are unlikely to be thoroughly characterized at a molecular level and will more likely need to be considered on an ad hoc basis.<sup>69</sup> Moreover, the EMA has issued six product-specific guidelines that address specific requirements for pre-clinical testing and clinical trials for recombinant erythropoietin, recombinant interferon alpha, low-molecular-weight-heparin, somatropin, human insulin, and granulocyte colony-stimulating factor.<sup>70</sup>

The second requirement of the EMA CHMP regulatory framework is a comparability study in order to demonstrate that a particular follow-on biologic is similar to the reference product in terms of quality, safety, and efficacy.<sup>71</sup> Indeed, neither the EU legislation creating an abbreviated approval pathway nor the EMA CHMP guidelines state a definition of a biosimilar other than that it is a protein product comparable in quality, safety, and efficacy to a reference product.<sup>72</sup>

Because the EMA CHMP has not defined precisely the acceptable level of differences between biosimilar and reference products in

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<sup>66</sup> See Schellekens & Moors, *supra* note 4, at 28.

<sup>67</sup> EMA, EMEA/CHMP/437/04, *supra* note 64, at 3.

<sup>68</sup> Wing Yan Tam, *supra* note 43, at 548 (citation omitted).

<sup>69</sup> EMA, EMEA/CHMP/437/04, *supra* note 64, at 6. As explained by one EMA scientist, pharmaceuticals can be arranged in terms of ascending order of complexity and difficulty of characterization as follows: chemicals; recombinant DNA technology; blood-derived; immunologicals, and advanced therapies. SUZETTE KOX, THE BIOSIMILAR FRAMEWORK IN THE EUROPEAN UNION 16 (2009), available at [http://www.egagenerics.com/doc/jga\\_symposium\\_2009-02-18\\_skox.pdf](http://www.egagenerics.com/doc/jga_symposium_2009-02-18_skox.pdf) (citing Dr. John Purves of the EMA).

<sup>70</sup> See *supra* note 64.

<sup>71</sup> See EMA, EMEA/CHMP/437/04, *supra* note 64, at 3. The reference product must itself have proceeded through the standard biological drug licensure process, not an abbreviated process. *Id.* Thus, one follow-on product cannot serve as a reference product for other follow-on biologics. *Id.*

<sup>72</sup> Schellekens & Moors, *supra* note 4, at 29.

terms of quality, safety, and efficacy, it is necessary to look to examples of biosimilar products for which the EMA CHMP permits use of the abbreviated approval pathway. The EMA has permitted biosimilars that have used completely different host cells, dissimilar formulations, differences in the levels of impurities, and variability in the levels of glycosylation.<sup>73</sup> According to Huub Schellekens and Ellen Moors, while these variations “are known to have the potential to have a major effect on a product’s clinical efficacy and safety,” clinical studies of biosimilars tested thus far have nonetheless demonstrated that “these differences have not compromised efficacy or influenced the level of adverse drug reactions in humans compared with the brand product.”<sup>74</sup>

The third EMA CHMP requirement for biosimilars is pharmacovigilance, which the World Health Organization (WHO) defines as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem” following the launch of a biological product on the market.<sup>75</sup> Indeed, in the EU, post-marketing monitoring is even required for new, innovative biologics, in light of the clinically meaningful differences between products and risk of immunogenicity.<sup>76</sup> As one expert noted, several factors, including the presence of impurities, structural modifications resulting from the manufacturing process or storage conditions, administration route, and patient characteristics, can all affect immunogenic potential and render it impossible to accurately predict immunogenicity in a patient.<sup>77</sup> For bio-

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<sup>73</sup> *Id.* “[I]t is the glycosylation of some proteins, which refers to ‘the variable attachment of small chains of sugars to the protein backbone,’ that renders glycosylated proteins more complex than nonglycosylated ones.” Gitter, *supra* note 4, at 560 n.19 (quoting David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 FOOD & DRUG L.J. 143, 224 (2005)).

<sup>74</sup> Schellekens & Moors, *supra* note 4, at 29. Interestingly, Schellekens and Moors point out that the technology used to produce follow-on protein products is in many cases superior to that of the reference products because brand manufacturers sometimes continue to employ old technologies in light of the significant financial and regulatory drawbacks involved in updating their production processes. *Id.* at 31; see *infra* note 126 and accompanying text.

<sup>75</sup> WORLD HEALTH ORG., WHO POLICY PERSPECTIVES ON MEDICINES: PHARMACOVIGILANCE: ENSURING THE SAFE USE OF MEDICINES 1 (Oct. 2004), available at <http://apps.who.int/medicinedocs/pdf/s6164e/s6164e.pdf>; see also Simoens, *supra* note 2, at 215 (“EMA guidelines also impose pharmacovigilance programmes to follow up safety and efficacy of biosimilars once approval has been gained.”).

<sup>76</sup> See Harrison, *supra* note 21, at 3 (“Biosimilars are required to undergo post-marketing monitoring just like new innovative biologics.”).

<sup>77</sup> See Ciftci, *supra* note 65.

similar in particular, pharmacovigilance is crucial because limited clinical data about safety risks tends to be available at the time of marketing authorization by the EMA due to the abbreviated approval pathway enjoyed by biosimilars.<sup>78</sup>

The EU established a pharmacovigilance program for all pharmaceuticals, chemical and biologic,<sup>79</sup> which includes several elements. First, a health-care professional can spontaneously report suspected adverse reactions to pharmaceuticals via the EudraVigilance network.<sup>80</sup> Second, the EMA often requires drug manufacturers, as part of the approval process, to develop and implement pharmacovigilance plans tailored to their particular products.<sup>81</sup> Such plans may include patient registries, along with retrospective and prospective observational and pharmacoepidemiological studies.<sup>82</sup> For instance, in 2003 the EMA approved the monoclonal antibody infliximab for the treatment of a particular inflammatory disease, ankylosing spondylitis, subject to the condition that the manufacturer conduct a follow-up clinical study to investigate the safety and efficacy of infliximab over a period of two years.<sup>83</sup>

In addition to submitting a pharmacovigilance plan, any applicant for market authorization for a new active substance, biosimilars included, must provide to the EMA a risk management plan (RMP),<sup>84</sup> which details “the actions and the surveillance that is undertaken to identify and manage potential safety risks.”<sup>85</sup> A RMP aims to be more proactive in risk management than a pharmacovigilance plan.<sup>86</sup> For example, to minimize the risk of infections following administration of natalizumab, a monoclonal antibody for relapsing multiple sclerosis,<sup>87</sup> the risk management plan imposed “a clear-cut definition of the

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<sup>78</sup> See Mellstedt et al., *supra* note 1, at 415.

<sup>79</sup> Volume 9A of The Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use (EU), Sept. 2008 [hereinafter Volume 9A], available at [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-9/pdf/vol9a\\_09-2008\\_en.pdf](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf).

<sup>80</sup> See Mellstedt et al., *supra* note 1, at 416.

<sup>81</sup> See *id.*

<sup>82</sup> See *id.*

<sup>83</sup> See Simoens, *supra* note 2, at 213.

<sup>84</sup> Volume 9A, *supra* note 79, at 38; see also Berthet-Maillols, *supra* note 45, at 112; Thijs Giezen et al., *Pharmacovigilance of Biosimilars from a Regulatory Point of View: Is There a Need for a Specific Approach?*, 21 INT'L J. RISK & SAFETY IN MED. 53, 55 (2009).

<sup>85</sup> See Simoens, *supra* note 2, at 213.

<sup>86</sup> See Giezen et al., *supra* note 84, at 55.

<sup>87</sup> *Questions and Answers on Natalizumab*, U.S. FOOD & DRUG ADMIN., Nov. 23, 2004, <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientandProviders/ucm107203.htm>.



target population, the requirement for established multiple sclerosis, an escape rule for non-responders, the administration in specialised centres by experienced physicians only, clear contraindications, a patient alert card, and an educational programme for physicians.”<sup>88</sup>

#### IV. REGULATORY AND POLICY ISSUES RAISED BY AN ABBREVIATED APPROVAL PATHWAY FOR BIOLOGICS IN LIGHT OF THE EU EXPERIENCE

For over five years the EU has relied on the abbreviated biosimilar pathway described above, which rests upon three essential requirements: (1) the provision of the requisite pre-clinical and clinical data; (2) a comparability exercise to show biosimilarity in quality, efficacy, and safety; and (3) product-specific pharmacovigilance and risk management plans to monitor potential immunogenicity. During this time, the major regulatory and policy issues that have arisen in that region include (1) how to assess comparability of the reference and follow-on biologic products; (2) whether to designate a biologic as interchangeable with the reference product; (3) the appropriate levels of immunogenicity testing, pharmacovigilance and risk assessment for biosimilars; (4) the propriety of giving a follow-on biologic the same name as the reference product; (5) the approval of a biosimilar drug for indications for which it has not been evaluated in clinical trials, based on extrapolation of data from the reference product; and (6) potential extensions to the term of data exclusivity for biosimilars. The FDA will need to consider each of these issues in developing guidance for manufacturers of follow-on biologics.

##### A. *The Challenge of Assessing Comparability*

The FDA must decide how to implement the “biosimilarity” designation, which requires that a product be “highly similar” to the reference product “notwithstanding minor differences in clinically inactive components.”<sup>89</sup> Among the questions the FDA must resolve is how much and what form of data will be required, including how much animal data and how much clinical data, in light of the agreement among most regulatory authorities that both pre-clinical and clinical data are needed to demonstrate the safety and efficacy of a biosimilar.<sup>90</sup> It is instructive, then, to analyze how the EU handles the issue of comparability for biosimilars. Indeed, some commentators

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<sup>88</sup> Simoens, *supra* note 2, at 213 (citations omitted).

<sup>89</sup> 42 U.S.C. § 262(k)(2)(A) (Supp. IV 2010); *see supra* notes 29–32 and accompanying text.

<sup>90</sup> *See* Ciftci, *supra* note 65 (citation omitted).

have noted that the EMA and the FDA have been working closely with one another, and FDA guidelines are likely to be based in large measure on the EMA's guidelines.<sup>91</sup>

While EMA guidelines indicate that "official data," such as pharmacopoeial monographs or other published scientific data, will be used initially to assess comparability, prior published information alone will not be adequate for approval, and "an extensive comparability exercise will be required" in order to demonstrate that the applicant drug and reference product have similar profiles in quality, safety, and efficacy.<sup>92</sup> The comparability exercise is typically performed through a "stepwise procedure" that begins with pharmacokinetic<sup>93</sup> and pharmacodynamic<sup>94</sup> studies, followed by clinical safety and efficacy trials, or, in certain cases, pharmacokinetic/pharmacodynamic studies for demonstrating clinical comparability.<sup>95</sup> The EMA emphasizes that pharmacokinetic studies "should not necessarily mimic" new drug application testing but instead, should focus on elucidating differences between the reference and biosimilar molecules.<sup>96</sup> For example, pharmacokinetic studies should explore differences in drug and reference biologic elimination from the body, and pharmacodynamic studies should compare the reference and biosimilar products in a population where possible clinical differences in the two products can best be observed.<sup>97</sup> As explained by the EMA, "it is not expected that the quality attributes in the similar biological and reference medicinal products will be identical," and it is expected that there will be "minor structural differences in the active substance, such as variability in post-translational modifications."<sup>98</sup> Thus, different amounts of pre-clinical and clinical data will be required on a case-by-case basis in order to ascertain the safety and efficacy of biosimilars.<sup>99</sup>

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<sup>91</sup> See Peter Gaskin, *Latest EU Guidelines Dissected*, PHARMACEUTICAL TECH. EUR., Aug. 2010, at 8, available at <http://www.pharmtech.com/ptedigital0810>.

<sup>92</sup> EMA, EMEA/CHMP/49348/2005, *supra* note 64, at 3.

<sup>93</sup> See *supra* note 20 (defining "pharmacokinetics").

<sup>94</sup> Pharmacodynamics is sometimes described as "what a drug does to the body" and "involves receptor binding, postreceptor effects, and chemical interactions." THE MERCK MANUALS, *supra* note 20. Pharmacodynamics, coupled with pharmacokinetics, elucidates a drug's effects on a person. *Id.*

<sup>95</sup> EMA, EMEA/CHMP/BWP/42832/2005, *supra* note 64, at 5.

<sup>96</sup> *Id.*

<sup>97</sup> *Id.*

<sup>98</sup> EMA, EMEA/CHMP/49348/2005, *supra* note 64, at 4.

<sup>99</sup> *Id.* at 4-5. The EMA states that the "differences between the impurity profiles of the similar biological medicinal product and the reference medicinal product

In terms of pre-clinical testing, the EMA guidelines indicate that pre-clinical testing may be abbreviated, although some testing must be performed. Pre-clinical testing should be truly comparative in nature and “designed to detect differences in response between the similar biological product and the reference medicinal product and not just the response *per se*.”<sup>100</sup> Such testing should include pharmacokinetic and pharmacodynamic studies.<sup>101</sup> Further, both *in vitro* and *in vivo* testing should be performed.<sup>102</sup> The EMA guidelines state that other “routine toxicological studies such as safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies” are not “normally” required.<sup>103</sup> Ultimately, the biosimilar applicant must justify its choice of pre-clinical studies performed and omitted.<sup>104</sup>

With respect to clinical testing, the EMA states that the requirements depend upon “the existing knowledge” about the reference product and its therapeutic indication.<sup>105</sup> Although the EMA acknowledges that manufacturing processes may change during the biologic development process, it recommends generating clinical data for comparability purposes with the biosimilar using the final manufacturing process and suggests that additional clinical testing requirements may be imposed if this recommendation is not fulfilled.<sup>106</sup> Just as for pre-clinical testing, justification of pharmacokinetic and pharmacodynamic testing approaches is required.<sup>107</sup>

Generally, clinical trials to demonstrate clinical comparability and efficacy should be performed once the necessary pharmacokinetic and pharmacodynamic assessments are complete.<sup>108</sup> But an abbreviated process may be available, and comparative pharmacokinetic and pharmacodynamic testing between the biosimilar and the reference biologic may be substituted for clinical studies if certain criteria are met, all of which relate to the extent to which the reference bi-

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should be justified and would be considered on a case-by-case basis” and that “differences in impurity profiles and significant differences in product related substances may have consequences with regard to the amount of non-clinical and clinical data which may be required.” *Id.*

<sup>100</sup> EMA, EMEA/CHMP/BWP/42832/2005, *supra* note 64, at 4.

<sup>101</sup> *Id.* at 4–5.

<sup>102</sup> *Id.* at 4.

<sup>103</sup> *Id.*

<sup>104</sup> *Id.*

<sup>105</sup> *Id.* at 5.

<sup>106</sup> EMA, EMEA/CHMP/BWP/42832/2005, *supra* note 64, at 5.

<sup>107</sup> *Id.*

<sup>108</sup> *Id.*

ologic's characteristics are well known.<sup>109</sup> In addition, product-specific guidelines are available for particular product classes of biosimilars.<sup>110</sup>

In order to assess how the EMA has implemented the comparability analysis with respect to a specific biosimilar, it is instructive to consider erythropoietin, which is used to treat anemia in patients with chronic kidney disease as well as patients receiving chemotherapy treatment for cancer.<sup>111</sup> Erythropoietin is recognized as one of the most difficult products for which to develop a biosimilar.<sup>112</sup> The EMA guidelines for erythropoietin state that comparability studies of clinical efficacy between the reference and biosimilar products should be performed in patients with anemia due to chronic renal disease.<sup>113</sup> In addition, the pharmacokinetic properties of the reference and biosimilar products should be compared for both routes of administration applied for, namely, intravenous and subcutaneous.<sup>114</sup> Current EMA guidelines also allow for extrapolation<sup>115</sup> of safety and efficacy data from patients with renal anemia to other indications of the reference product with the same route of administration if the extrapolation can be appropriately justified.<sup>116</sup>

It should be noted that while the EMA has approved fourteen of the eighteen biosimilar applications submitted to it, it has rejected one, and three applications for other biosimilars have been withdrawn by their manufacturers because of the likelihood that they would not be approved due to lack of comparability.<sup>117</sup> In 2006, the EMA rejected the application for marketing approval for Alpheon, a

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<sup>109</sup> *Id.* at 5–6.

<sup>110</sup> *See supra* note 64.

<sup>111</sup> *See* Mellstedt et al., *supra* note 1, at 414.

<sup>112</sup> *See id.* at 415.

<sup>113</sup> *See id.*

<sup>114</sup> EMA, EMEA/CHMP/BMWP/301636/2008, *supra* note 64, at 5.

<sup>115</sup> Extrapolation “involves the approval of a drug for indications for which it has not been evaluated in clinical trials.” Mellstedt et al., *supra* note 1, at 417. The EMA has generally accepted the concept of data extrapolation for biosimilars “with the appropriate justification.” *Id.*

<sup>116</sup> EMA, EMEA/CHMP/BMWP/301636/2008, *supra* note 64, at 8.

<sup>117</sup> E-mail from Anna Nagielska, Document and Information Services, European Medicines Agency, to author (July 23, 2010, 06:47 EST) (on file with author); *see also* EMA, *Questions and Answers on the Withdrawal of the Marketing Authorisation Application for Insulin Human Rapid Marvel, Insulin Human Long Marvel, Insulin Human 30/70 Mix Marvel*, at 1, EMEA Doc. No. 4193/2008 (Jan. 24, 2008), available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Medicine\\_QA/2009/11/WC500015341.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/11/WC500015341.pdf).

biosimilar version of a branded interferon product.<sup>118</sup> The manufacturer of Alpheon submitted pre-clinical data on the biosimilar and also conducted a randomized controlled trial in 455 patients with hepatitis C to demonstrate comparability with the reference product.<sup>119</sup> The EMA rejected the application due to, among other factors, quality and clinical differences between Alpheon and the reference product, inadequate data on the stability of the active substance, inadequate validation of the process for the finished product, and insufficient validation of immunogenicity testing.<sup>120</sup>

While the EMA process for approving biosimilars is generally recognized as a success, Schellekens and Moors question the EMA CHMP requirement for comparability studies, as a complement to the necessary clinical data.<sup>121</sup> According to Schellekens and Moors, “the merits and/or added value of the comparability exercise are questionable” for several reasons.<sup>122</sup> First, they contend that the improvement of analytical tools means that the ability to find differences between reference and follow-on products will only increase, while, in most cases, the consequences of these differences remain unknown.<sup>123</sup> What is more, such differences are irrelevant if the clinical data shows the products to be clinically equivalent.<sup>124</sup>

Second, Schellekens and Moors note that biosimilar manufacturers actually use state-of-the-art technology, while older technologies often constrain brand manufacturers because of the costs and regulatory hurdles involved in updating their practices.<sup>125</sup> Thus, they maintain that “it seems much more logical for regulators to expect biosimilars to be produced by the best technology on offer rather than to mandate that they are made of comparable quality to the brands.”<sup>126</sup>

Third, according to Schellekens and Moors, comparative pharmacokinetic trials are of limited usefulness for many reasons. For example, “the acceptance range for pharmacokinetics parameters be-

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<sup>118</sup> EMA, *Questions and Answers on Recommendation for Refusal of Marketing Application for Alpheon*, at 1, EMEA Doc. No. 190896/2006 (June 28, 2006), available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Summary\\_of\\_opinion\\_-\\_Initial\\_authorisation/human/000585/WC500017451.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/000585/WC500017451.pdf).

<sup>119</sup> *Id.*

<sup>120</sup> *Id.* at 2.

<sup>121</sup> Schellekens & Moors, *supra* note 4, at 30–31.

<sup>122</sup> *Id.* at 30.

<sup>123</sup> *Id.*

<sup>124</sup> *Id.*

<sup>125</sup> *Id.* at 31.

<sup>126</sup> *Id.*

tween biosimilar and reference product are difficult or impossible to predefine and justify,” and the relationships between such parameters and actual clinical effects are unclear.<sup>127</sup>

Thus, Schellekens and Moors advocate the end of the regulatory requirement for a comparability exercise for biosimilars.<sup>128</sup> They acknowledge that comparisons between reference and follow-on biologics are useful during the development of biosimilars to set specifications for production and purification, to validate production methods and analytical tools, for marketing purposes, and perhaps to claim extrapolation of an indication.<sup>129</sup> Nonetheless, they believe that discontinuation of the comparability exercise will hasten the creation of biosimilars that are more complex.<sup>130</sup> At present, however, the comparability exercise remains firmly entrenched as a regulatory requirement for approval of follow-on biologics.

*B. The Difficulty of Assessing Interchangeability of the Reference and Biosimilar Products*

Once a biosimilar product has been adjudged comparable to the reference product, it can also be evaluated for interchangeability. According to the BPCIA, a biological product is acknowledged to be interchangeable with a reference product if it is biosimilar to the reference product and “can be expected to produce the same clinical result as the reference product in any given patient.”<sup>131</sup> A pharmacy can then substitute interchangeable products in place of a branded product without the knowledge or approval of a physician.<sup>132</sup>

The BPCIA is unique in providing a means of approving a follow-on biologic either as a “stand-alone product” or as interchangeable with a reference product.<sup>133</sup> The EMA has taken the position,

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<sup>127</sup> Schellekens & Moors, *supra* note 4, at 30–31.

<sup>128</sup> *Id.*

<sup>129</sup> *Id.*

<sup>130</sup> *Id.*

<sup>131</sup> 42 U.S.C. § 262(k)(4)(A)(ii) (Supp. IV 2010). Furthermore, if a biological product “is administered more than once to an individual,” it will be deemed interchangeable only if “the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.” § 262(k)(4)(B).

<sup>132</sup> *See* § 262(k)(4). The term “interchangeability” has a similar meaning in the EU. *See* Mellstedt et al., *supra* note 1, at 416 (“Automatic substitution allows for the dispensing of generic drugs in place of prescribed innovator products by pharmacists without the knowledge or consent of the treating physician.”).

<sup>133</sup> *Cf.* Ywe J. Looper, *Legislative Initiatives in Europe, Canada and the United States for Market Authorization of Follow-on Biologics*, 13 CURRENT OPINION IN DRUG DISCOVERY &

through its Executive Director Thomas Lonngren, that “[i]t is not possible [the EMA] would guarantee a biosimilar is interchangeable (with its originator).”<sup>134</sup> Instead, substitution is a matter for regulators in each individual member nation.<sup>135</sup> Although Lonngren concedes that the EMA’s scientists are probably best placed to decide if a biosimilar is similar enough to its reference product to be substitutable, he notes that the authority to answer this question has traditionally belonged to national health systems, and, therefore, remains outside the EMA’s remit.<sup>136</sup> Indeed, an official EMA statement in 2007 declared that “[s]ince biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified health-care professional.”<sup>137</sup>

Experts have noted several reasons why automatic substitution is not appropriate for biologics, even though some U.S. states and EU nations do permit automatic substitution for certain traditional chemical pharmaceuticals.<sup>138</sup> First, “biosimilars are not generic versions of innovator products, and there will be limited clinical experience with biosimilars at the time of approval,” and “[s]mall differences between biosimilars and innovator products may affect clinical outcomes.”<sup>139</sup> Moreover, if countries permit automatic substitution, patients could receive multiple biopharmaceutical products over the course of a therapy, making it difficult to determine the cause of any adverse events.<sup>140</sup>

Recently, both France and Spain enacted legislation banning the automatic substitution of biosimilars for branded products without

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DEV. 247, 252 (2010) (discussing the United States’ unique approach to interchangeability in the context of draft biosimilar legislation that was previously proposed in the United States).

<sup>134</sup> Nick Smith, *EMA “Will Not Guarantee” That Biosimilars Are Interchangeable With Originator*, APM HEALTH EUROPE, July 21, 2006, <http://www.apmhealthurope.com/depechesPublieesDepeches.php?annee=2006&mois=7&jour=21> (citing EMA Executive Director Thomas Lonngren).

<sup>135</sup> *See id.*

<sup>136</sup> *Id.*

<sup>137</sup> EMA, *Questions and Answers on Biosimilar Medicines (Similar Biological Medicinal Products)*, at 1, EMEA Doc. No. 74562/2006 (Apr. 19, 2007), available at [www.ebiopharma.org/documents/biosimilars/biosimilars\\_q+and+a.pdf](http://www.ebiopharma.org/documents/biosimilars/biosimilars_q+and+a.pdf).

<sup>138</sup> Mellstedt et al., *supra* note 1, at 416. Indeed, mandatory substitution laws in many U.S. states require pharmacists, when presented with a brand-name prescription, to substitute it with the generic version. *See* John A. Vernon et al., *Exploration of Potential Economics of Follow-on Biologics and Implications for Data Exclusivity Periods for Biologics*, 16 B. U. J. SCI. & TECH. L. 55, 67 (2010).

<sup>139</sup> Mellstedt et al., *supra* note 1, at 416.

<sup>140</sup> *Id.*

the express consent of the prescribing physician.<sup>141</sup> Research has not revealed any instance of an EU member state approving the automatic substitution of a biologic. Concomitantly, some U.S. commentators express doubt that the FDA will designate follow-on biologics as interchangeable with reference products and suggest that follow-on products will “[m]ost likely will be treated as therapeutic alternatives by health care providers, which will limit their uptake in the market relative to generic pharmaceuticals.”<sup>142</sup> Another open question in the United States is whether there will be a federal determination of interchangeability as opposed to a decision at the state level.

It is interesting to note, however, that, notwithstanding the French legislature’s ban on any substitute for biosimilars without the express consent of the prescribing physician,<sup>143</sup> three French medical societies relating to nephrology seek to foster substitutability for biosimilars as a means of better serving their patients.<sup>144</sup> These groups have considered the creation of a “biosimilar repertory,” which would allow for a period of two to three years to study the use of biosimilars prescribed to treat kidney disease, and gather the appropriate pharmacovigilance data.<sup>145</sup> The repertory would ultimately permit substitution by the pharmacist “on the condition that the doctor hasn’t specified on the prescription that the prescribed product isn’t substitutable.”<sup>146</sup> In praising this possibility, Elisabeth Berthet-Maillols expresses skepticism that any ban on substitutability is free from influence from the concerned innovator labs, which have a strong stake in preventing substitution.<sup>147</sup>

C. *The Establishment of Immunogenicity Testing, Pharmacovigilance, and Risk Management Plans*

EMA guidelines require immunogenicity testing and pharmacovigilance programs to monitor the efficacy and safety of biosimilar products post-approval.<sup>148</sup> Post-approval safety testing is particularly

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<sup>141</sup> C. Fernandez et al., *Biosimilars: What Pharmacists Need to Know*, 15 EUR. J. HOSP. PHARMACY PRAC. 41, 43 (2009); Schellekens, *supra* note 7, at i32. While seven other E.U. member nations also ban automatic substitution, they in fact do so for all pharmaceuticals, both chemical and biological.

<sup>142</sup> Vernon et al., *supra* note 138, at 67.

<sup>143</sup> See Schellekens, *supra* note 7, at i32.

<sup>144</sup> See Berthet-Maillols, *supra* note 45, at 124.

<sup>145</sup> *Id.*

<sup>146</sup> *Id.* (citation omitted).

<sup>147</sup> See *id.*

<sup>148</sup> See *supra* notes 64–65 and accompanying text.



important with respect to biosimilars because there is limited clinical data available at the time of their approval since comprehensive clinical testing is often not required.<sup>149</sup> Moreover, pharmacovigilance programs are useful in terms of assessing product safety for specific patient populations, which is particularly important for the safe use of biosimilars in therapeutic indications for which the product may not have been formally evaluated, such as for an extrapolated indication.<sup>150</sup>

The importance of post-marketing pharmacovigilance is highlighted by Johnson & Johnson's Eprex, a blockbuster erythropoietin-reference product, which gave rise to the potentially fatal condition of pure red cell aplasia in patients after a formulation change.<sup>151</sup> In addition, after the approval of the biosimilar-growth hormone Omnitrope, immunogenicity issues arose. During development, production of Omnitrope had been transferred from one manufacturing facility to another.<sup>152</sup> Although qualitative testing demonstrated no significant differences between the end products of these facilities, the products exhibited different immunogenicity profiles, an occurrence that the manufacturer was able to rectify prior to approval.<sup>153</sup>

Both the EMA in the EU and the FDA in the United States have established rigorous pharmacovigilance programs for the monitoring of adverse events relating to all medicinal products, not only biosimilars.<sup>154</sup> As explained by Laura Faden and Christopher-Paul Milne, both regions have implemented procedures for post-marketing surveillance (PMS), post-approval research (PAR), and risk management.<sup>155</sup> PMS involves collecting information on outcomes from medical professionals, patients, and manufacturers, either passively, such as through reports of adverse events, or actively, via data-mining of health records from third-party payers or registries.<sup>156</sup> PAR encompasses follow-up studies or surveys aimed at determining the magnitude and frequency of adverse events related to a particular medicinal product and attempts to discern whether reported adverse health

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<sup>149</sup> See Mellstedt et al., *supra* note 1, at 415.

<sup>150</sup> See *id.* at 415–16.

<sup>151</sup> See Gitter, *supra* note 4, at 605–06.

<sup>152</sup> See Mellstedt et al., *supra* note 1, at 414–15.

<sup>153</sup> See *id.*

<sup>154</sup> See Laura B. Faden & Christopher-Paul Milne, *Pharmacovigilance Activities in the United States, European Union, and Japan: Harmonic Convergence of Convergent Evolution?*, 63 FOOD & DRUG L.J. 683, 683–84 (2008).

<sup>155</sup> *Id.* at 684–85.

<sup>156</sup> *Id.*

effects are actually causally related to the product under investigation.<sup>157</sup> Risk management entails the use of PMS and PAR data to develop means of preventing or reducing the potential risks that medicinal products pose and may include planning, education, and communication measures.<sup>158</sup>

Experts have noted two significant differences, however, between pharmacovigilance in the EU and the United States. First, PMS in Europe is “more inclusive” than in the United States with respect to “compiling adverse event reports and data from sources worldwide” and has traditionally advocated “a more compulsory approach toward assessment of data” for signs of adverse events.<sup>159</sup> Second, with respect to biosimilars in particular, the EU requires a risk management plan (RMP) for all biosimilars that receive approval through the centralized procedure<sup>160</sup> as well as for all drugs with new active ingredients.<sup>161</sup> For example, the EU RMP for all erythropoietin biosimilars provides that, with respect to risks of thrombotic-vascular events, the Summary of Product Characteristics (SMPC), which is submitted with the application for marketing authorization and provides information for medical professionals as to the use of the product,<sup>162</sup> should state that the target hemoglobin not exceed 12 g/dl.<sup>163</sup> With respect to the increased incidence of pure red cell aplasia with off-label subcutaneous use in renal-failure patients, the EU RMP provides for the creation of an SMPC that warns of this risk and for the widespread distribution of an educational leaflet to health-care providers.<sup>164</sup>

The United States is increasingly harmonizing its approach to post-market safety in accordance with the EU approach, however, in light of its newly adopted abbreviated-approval pathway for biosimilars that tracks the EU system. Drug sponsors, who frequently seek

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<sup>157</sup> *Id.*

<sup>158</sup> *Id.*

<sup>159</sup> *Id.* at 697.

<sup>160</sup> See *supra* note 61 and accompanying text for a discussion of the EU’s centralized regulatory process.

<sup>161</sup> See Faden & Milne, *supra* note 154, at 697; see also EMA, *Guideline on Risk Management Systems for Medicinal Products for Human Use*, at 7, EMEA Doc. No. CHMP/96268/2005 (Nov. 14, 2005), available at <http://web.invima.gov.co/portal/documents/BVSalud/IVC/anexo5emeagrmsmp.pdf>.

<sup>162</sup> EUROPEAN COMM’N, ENTER. & INDUS. DIRECTORATE-GEN., A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS 1 (Oct. 2005), available at [http://ec.europa.eu/health/files/eudralex/vol-2/c/spcguidrev1-oct2005\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-2/c/spcguidrev1-oct2005_en.pdf).

<sup>163</sup> See Berthet-Maillols, *supra* note 45, at 120.

<sup>164</sup> See *id.* at 120–21.

approval in both regions, favor harmonization.<sup>165</sup> The U.S. Food and Drug Administration Amendments Act of 2007<sup>166</sup> minimizes the gap between the EU, which requires comprehensive post-marketing safety data, and the United States, which traditionally has not, by granting the FDA the authority to require manufacturers to collect patient safety data in the form of a Risk Evaluation and Mitigation Strategy (REMS).<sup>167</sup> The FDA will require a REMS, an analogue to the EU RMP,<sup>168</sup> if the FDA determines that a risk-management approach is necessary in order to ascertain that the benefits of the product outweigh its risks.<sup>169</sup> Nonetheless, in contrast to the EU, a REMS is required in the United States only if the FDA determines that it is necessary.<sup>170</sup> Generally, the FDA does not require a REMS if a product's labeling is adequate to establish that the benefits for that user outweigh its risks.<sup>171</sup>

Harmonization efforts operate on an international level as well. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, which is made up of regulatory bodies, pharmacopeias, and drug-industry members from the United States, Europe, and Japan, has created a guidance document on pharmacovigilance planning for drugs approved in the United States, EU, and Japan.<sup>172</sup>

The pharmacovigilance and risk-management processes relating to biosimilars loom very large because of the safety concerns that biosimilars in developing nations raise.<sup>173</sup> Berthet-Maillols notes, however, that similar issues have not arisen with biosimilars that the EMA

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<sup>165</sup> See Faden & Milne, *supra* note 154, at 696.

<sup>166</sup> Pub. L. No. 110-185, 121 Stat. 926.

<sup>167</sup> See Faden & Milne, *supra* note 154, at 687.

<sup>168</sup> See Cheryl Key et al., *The Value of Reviewing Existing EU Risk Management Plans*, RAJ PHARMA, Feb. 2010, at 79, available at <http://www.quintiles.com/elements/media/inthenews/reviewing-existing-risk-management-plans.pdf>.

<sup>169</sup> See Faden & Milne, *supra* note 154, at 687.

<sup>170</sup> See *id.*

<sup>171</sup> See Key et al., *supra* note 168, at 79.

<sup>172</sup> INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE, E2E: PHARMACOVIGILANCE PLANNING (2002), available at [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/E2E/Concept\\_papers/E2E\\_Concept\\_Paper.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/E2E/Concept_papers/E2E_Concept_Paper.pdf); see also Faden & Milne, *supra* note 154, at 696; Agnes Shanley, *Taking the Plunge to Harmonize Pharmaceutical Regulations*, PHARMAMANUFACTURING.COM (Mar. 2010), <http://www.pharmamanufacturing.com/articles/2010/034.html>.

<sup>173</sup> See Schellekens, *supra* note 7, at i31 (describing an immunogenic response in a patient using a follow-on epoetin manufactured in India).

has authorized, thereby demonstrating that such products are indeed safe when vetted via a rigorous approval process.<sup>174</sup>

*D. The Naming of Follow-On Biological Products*

The WHO provides guidance for naming biologic products. The WHO grants each pharmaceutical substance an International Nonproprietary Name (INN), or generic name,<sup>175</sup> guided by an international expert advisory panel.<sup>176</sup> According to the WHO, “INN[s] are selected in principle only for single, well-defined substances that can be unequivocally characterized by a chemical name (or formula)”; they are not given to mixtures of substances or substances that are not well-characterized.<sup>177</sup> Generic chemical drugs typically receive the same INN as the reference drug because “the active ingredient of the generic is considered to be an exact copy of the active ingredient of the reference drug.”<sup>178</sup>

Similarly, the WHO has determined that INNs should be given to biosimilars based on their active ingredient, provided the assessment of active ingredient is sufficiently consistent and precise.<sup>179</sup> Thus, even though biologics are not well-characterized, the WHO notes that INNs have “been assigned to biological medicines since the early days of the programme, including biotechnology derived products such as monoclonal antibodies and a range of recombinant DNA derived proteins.”<sup>180</sup> For example, the brand name forms of human growth hormone, Genotrope and Humatrope, share the same INN: somatropin.<sup>181</sup> In addition, the biosimilars that used these branded forms as their reference molecules, Omnitrope and Valtropin, also share that same INN.<sup>182</sup>

INNs are intended for use in pharmacopoeias, labeling, product information, advertising and other promotional material, drug regu-

<sup>174</sup> See Berthet-Maillols, *supra* note 45, at 119.

<sup>175</sup> *Medicines: International Nonproprietary Names*, WORLD HEALTH ORG., <http://www.who.int/medicines/services/inn/en> (last visited Mar. 2, 2011).

<sup>176</sup> Mellstedt et al., *supra* note 1, at 416.

<sup>177</sup> *Guidance on INN*, WORLD HEALTH ORG., <http://www.who.int/medicines/services/inn/innguidance/en/index.html> (last visited Mar. 2, 2011).

<sup>178</sup> CHU & PUGATCH, *supra* note 15, at 12 n.29.

<sup>179</sup> WORLD HEALTH ORG., *INFORMAL CONSULTATION ON INTERNATIONAL NONPROPRIETARY NAMES (INN) POLICY FOR BIOSIMILAR PRODUCTS 4–6 (2006)*, available at [http://www.who.int/medicines/services/inn/BiosimilarsINN\\_Report.pdf](http://www.who.int/medicines/services/inn/BiosimilarsINN_Report.pdf).

<sup>180</sup> *Id.* at 5.

<sup>181</sup> See Liang, *supra* note 17, at 424.

<sup>182</sup> See *id.* Although biosimilars share the same INN as the reference product, they are required to have a separate trade name. See CHU & PUGATCH, *supra* note 15, at 21.

lation and scientific literature, and as a basis for generic product names. Jurisdictions such as the EU, Japan, and the United States have agreed to harmonize, in large measure, their naming of biopharmaceuticals through the adoption of INNs.<sup>183</sup> Once it assigns an INN, the WHO formally places it in the public domain, which renders that INN truly nonproprietary and means that the INN can be used without any restriction whatsoever to identify pharmaceutical substances.<sup>184</sup>

There is debate with respect to the attribution of INNs to biological products among WHO officials, as well as among manufacturers of reference and follow-on products, professional medical societies, and academics.<sup>185</sup> In a 2006 consultation paper summarizing a meeting between WHO officials and representatives of various national regulatory agencies, the WHO asserted that “the concept of a biosimilar product is regulatory in nature, whereas assignment of an INN is a nomenclature process based on scientific characterization of an active pharmaceutical substance.”<sup>186</sup> The WHO noted that there was “complete agreement amongst the national regulatory authorities present,” including from the EU EMA and the U.S. FDA, that “[t]he assignment of INNs should be independent of the regulatory process or of considerations of prescribing interchangeability or the use of INNs in pharmacovigilance.”<sup>187</sup> Therefore, “it was recommended that no distinctive designation to indicate the regulatory term biosimilar be built into the INN for these products. Instead, it was proposed that INN policy for naming biosimilars be the same as that for stand alone biologicals.”<sup>188</sup> One caveat to this recommendation, however, is that differences in glycosylation<sup>189</sup> have been handled by giving an INN name that adds a Greek letter spelled out as a second word (for example, epoetin alpha, epoetin beta).<sup>190</sup>

Various scholars have suggested, however, that the pharmacovigilance process would benefit from the assignment of unique INNs to biopharmaceuticals because it would facilitate accurate prescribing and dispensing and properly link any adverse event to the specific

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<sup>183</sup> WORLD HEALTH ORG., *supra* note 179, at 5.

<sup>184</sup> *Id.*

<sup>185</sup> See Berthet-Maillols, *supra* note 45, at 121–22 (describing the debate among many stakeholders concerned about the INN process).

<sup>186</sup> WORLD HEALTH ORG., *supra* note 179, at 7.

<sup>187</sup> *Id.* at 10.

<sup>188</sup> *Id.*

<sup>189</sup> See *supra* note 73 and accompanying text.

<sup>190</sup> WORLD HEALTH ORG., *supra* note 179, at 5–6.

product. For example, three prominent European oncologists suggest that the WHO ought to “assign unique INNs to biopharmaceuticals.”<sup>191</sup> Likewise, Schellekens contends that “[u]nique naming for all biopharmaceuticals would likely help to differentiate these products, which would facilitate accurate prescribing, dispensing and pharmacovigilance.”<sup>192</sup>

Other experts disagree with the notion of unique naming for biopharmaceuticals, so as to differentiate each biosimilar product from its reference product and from other follow-on protein products. According to Berthet-Maillols, once the comparability exercise has been performed and a marketing authorization has been granted, “it would be scientifically inconsistent to ask a company to apply for a different INN for a biosimilar product.”<sup>193</sup> By that logic, the reference product would itself require a new INN each time it was not found to be identical to its earlier formulation.<sup>194</sup>

Berthet-Maillols also notes that the EMA regulations already require that biosimilars be prescribed by their approved names, meaning either their trade name or a scientific denomination accompanied by a trademark, or by the holder of the marketing authorization.<sup>195</sup> Furthermore, side effects must be reported by identifying the name of the medicinal product and the batch number, not simply an INN. She cites one study, performed before batch numbers were required to accompany reports of side effects, showing that of 8970 reports concerning the biologic drug erythropoietin, doctors had included the full product name, rather than merely the INN, ninety-nine percent of the time.<sup>196</sup> Thus, Berthet-Maillols concludes that “[d]octors seem to have integrated on their own the necessity, regarding the traceability of biotechnology medicines” by mentioning the full product name and not only the INN;<sup>197</sup> therefore, “the attribution of an INN different from that of the [reference product] for each of its biosimilars does not seem to be necessary in the name of ensuring the pharmacovigilance of biotechnology products.”<sup>198</sup>

Experts also argue that, in addition to unique naming, more comprehensive labeling of biosimilars would assist physicians and

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<sup>191</sup> Mellstedt et al., *supra* note 1, at 416.

<sup>192</sup> Schellekens, *supra* note 7, at i34.

<sup>193</sup> Berthet-Maillols, *supra* note 45, at 122 (citations omitted).

<sup>194</sup> *Id.*

<sup>195</sup> *Id.*

<sup>196</sup> *Id.*

<sup>197</sup> *Id.*

<sup>198</sup> *Id.*

pharmacists in decision-making. According to Mellstedt et al., “[b]ecause biosimilars are not equivalent to reference products and because unique efficacy and safety data will be available, labeling should include these data . . . [and] those indications that are based upon extrapolation of data.”<sup>199</sup> Schellekens agrees that “[t]he labels of the approved biosimilars are nearly identical or are very similar to those of the reference product. A more transparent label that included relevant clinical data for the biosimilar, such as the data included in EPAR [European Public Assessment Reports], would help clinicians make informed treatment decisions.”<sup>200</sup>

*E. Extrapolation of Indications*

Extrapolation of indications is another issue facing the FDA as it develops an abbreviated approval pathway for biosimilars. An “[e]xtrapolation involves the approval of a drug for indications for which it has not been evaluated in clinical trials.”<sup>201</sup> The EMA generally supports data extrapolation for biosimilars that make the requisite scientific showing on the theory that if the biosimilar shows adequate comparability to the reference product for one indication, it may be reasonable to extend the biosimilar’s approval to other indications of the innovator product.<sup>202</sup>

The EU’s current guidance with respect to biosimilars provides that if a reference product “has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.”<sup>203</sup> But “[i]n certain cases it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal product.”<sup>204</sup> A sufficient showing will depend, inter alia, on clinical experience, available literature and data, and whether the same mechanisms of action or the same receptor(s) are involved in all indications.<sup>205</sup> If the mechanism of action differs between indications, the biosimilar manufacturer may be

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<sup>199</sup> Mellstedt et al., *supra* note 1, at 416.

<sup>200</sup> Schellekens, *supra* note 7, at i34. EPARs are assessment reports for the evaluation of marketing authorization applications made public by the EMA on its website. Key et al., *supra* note 168, at 80.

<sup>201</sup> Mellstedt et al., *supra* note 1, at 417.

<sup>202</sup> *Id.*

<sup>203</sup> EMA, EMEA/CHMP/BWP/42832/2005, *supra* note 64, at 3.

<sup>204</sup> *Id.*

<sup>205</sup> *See id.*

required to provide additional clinical data.<sup>206</sup> One example of extrapolation involves the biosimilar human growth hormone Omnitrope and its reference product Genotropin.<sup>207</sup> Although efficacy and safety studies between the two products were conducted only in children with growth disorders, the product labeling for Omnitrope is “virtually identical to that of the reference product, including the indication for use in adults.”<sup>208</sup>

As Mellstedt notes, although extrapolation is appropriate for well-characterized proteins such as human growth hormones, it may not apply in cases involving more complex biopharmaceutical products or high-risk populations.<sup>209</sup> This issue will be especially important for the development of monoclonal antibodies, which are very complex biopharmaceuticals that constitute the fastest-growing sector of the biopharmaceutical industry and for which many initial patents will expire in 2014.<sup>210</sup>

*F. The Possibility of Extensions to the Term of Data Exclusivity*

As noted previously, the EU affords ten years of data exclusivity to biologics that have received a marketing authorization.<sup>211</sup> In addition, an innovator may obtain an additional year of data exclusivity if it obtains authorization for new therapeutic indication(s) which bring(s) significant clinical benefits in comparison with existing therapies.<sup>212</sup> The EU considers the initial marketing authorization in Europe to be a “global marketing authorization, which covers all variations in drug strength, formulation, route of administration, or change in manufacturing procedure that are subsequently authorized to the original licensor.”<sup>213</sup> Thus, “all of these variations are considered to have a single period of data exclusivity that is timed from the initial market authorization.”<sup>214</sup>

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<sup>206</sup> See Mellstedt et al., *supra* note 1, at 417.

<sup>207</sup> *See id.*

<sup>208</sup> *Id.*

<sup>209</sup> *Id.*

<sup>210</sup> See Ciftci, *supra* note 65.

<sup>211</sup> *See supra* note 45 and accompanying text.

<sup>212</sup> *See supra* note 46 and accompanying text.

<sup>213</sup> Looper, *supra* note 133, at 253.

<sup>214</sup> *Id.* (citing Directive 2004/27/EC, of the European Parliament and of the Council of 31 March 2004 Amending Directive 2001/83/EC on the Community Code Relation to Medicinal Products for Human Use—Amendment to Article, 2004 O.J. (L136) 34, 34–57.).



Like the EU regulatory scheme, the BPCIA does not provide for renewal of data exclusivity in favor of a sponsor of a reference product in case of changes in drug strength, formulation, or route of administration.<sup>215</sup> Despite this similarity, the BPCIA also differs from EU law in a few significant ways. First, the BPCIA does not provide for renewal of data exclusivity for an innovator firm in case of changes in indication.<sup>216</sup> Second, the BPCIA will consider the renewal of data exclusivity in the case of a structural modification to a reference product that results in a change in safety, purity, or potency compared to the original product.<sup>217</sup>

Looper notes that “[t]he eligibility of a second-generation biological product with structural modifications (e.g., PEGylation or glycosylation) and concomitant improvements in efficacy, safety or release profiles for consideration as a distinct biological product for the purposes of data protection in Europe . . . has not been established.”<sup>218</sup> Because second-generation biological products that have obtained market authorization as follow-on biologics cannot be used as reference products by manufacturers of future follow-on biologics,<sup>219</sup> there is limited social value in permitting makers of follow-on biologics to obtain data exclusivity.

This may change, however. As Falk Ehmann of the EMA notes, the EMA must consider whether the regulatory pathway for biosimilars may be a two-way street, that is, whether such that a reference product would ultimately be able to refer to characteristics of its counterpart biosimilar, such as the biosimilar’s dosing, route of administration, and indication.<sup>220</sup> Such an approach would undoubtedly expedite the drug development and approval process, redounding to the benefit of consumers.

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<sup>215</sup> 42 U.S.C. § 262(k)(7)(C) (Supp. IV 2010).

<sup>216</sup> Looper, *supra* note 133, at 253.

<sup>217</sup> § 262(k)(7)(C).

<sup>218</sup> Looper, *supra* note 133, at 253.

<sup>219</sup> *Id.* at 248 (stating that EU law requires a reference product “to have received market authorization through the standard drug licensure process”). In the United States as well, a reference product must have been approved in the United States. *See* § 262(i)(3).

<sup>220</sup> FALK EHMANN, BIOSIMILARS IN THE EUROPEAN UNION—EXPERIENCE GAINED AND PERSPECTIVES 32 (2008), *available at* <http://www.biosimilarstoday.com/2008/Ehmann.pdf>.

## V. CONCLUSION

With the enactment of the Biologics Price Competition and Innovation Act of 2009, the U.S. FDA will issue guidance for manufacturers of follow-on biologics. Foremost among the issues faced by the FDA are the assessment of comparability of the reference and follow-on biologic products; the interchangeability of the follow-on and reference products; the appropriate levels of immunogenicity testing, pharmacovigilance and risk assessment for biosimilars; the naming of follow-on biologics; the approval of a biosimilar drug for indications for which it has not been evaluated in clinical trials, based on extrapolation of data from the reference product; and potential extensions to the term of data exclusivity for biosimilars. These issues have been, or presently are, under discussion in the EU.

While the United States will certainly look to the EU in developing its abbreviated pathway, with the passage of time, the EU will be influenced by developments in the United States, thereby fostering harmonization between the jurisdictions. For example, the BPCIA allows for the possibility of the renewal of data exclusivity in the case of a structural modification to a reference product that results in a change in safety, purity, or potency compared to the original product. This possibility creates an incentive to develop second-generation follow-on protein products. If, along with this provision, legislation were enacted that would permit a reference product to rely on data produced by the manufacturer of the follow-on product, this reliance would create a feedback loop that would dramatically expedite biosimilar drug development and the approval process. In this way, the BPCIA could truly revitalize the biosimilar industry, which would contribute immeasurably to public health.