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MUTUAL RECOGNITION OF MANUFACTURING PRACTICES BETWEEN THE EUROPEAN MEDICINES AGENCY AND THE FOOD AND DRUG ADMINISTRATION: THE GROUNDWORK FOR THE MUTUAL RECOGNITION OF BIOSIMILARS

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**MUTUAL RECOGNITION OF MANUFACTURING
PRACTICES BETWEEN THE EUROPEAN MEDICINES
AGENCY AND THE FOOD AND DRUG
ADMINISTRATION: THE GROUNDWORK FOR THE
MUTUAL RECOGNITION OF BIOSIMILARS**

*Katerina U**

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I. INTRODUCTION

The 2017 Amended Sectoral Annex to the 1998 US-EU Mutual Recognition Agreement (“2017 Amended US-EU MRA”) became effective in November 2017, bridging a transatlantic regulatory gap between the United States (“US”) and the European Union (“EU”).¹ Although the Mutual Recognition Agreement (“MRA”) applies specifically to manufacturing facility inspections,² it is a giant leap toward international harmonization of regulatory standards.

This Note will first explore how the Food and Drug Administration (“FDA”) came into its regulatory authority in the United States.³ The current drug approval processes will be summarized with a focus on biological products and their link to manufacturing regulations.⁴ Next,

1. Press Release, EMA, EU-US Mutual Recognition of Inspections of Medicines Manufacturers Enters Operational Phase (Oct. 31, 2017), http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2017/10/WC500237909.pdf [hereinafter *EU-US Mutual Recognition of Inspections*].

2. *Id.*

3. *See infra* Part II.A.

4. *See infra* Part II.B.

this Note will take a comparative look at the European Medicines Agency (“EMA”) and their processes for drug market approval.⁵ Then, the 2017 Amended US-EU MRA and its implications will be examined.⁶ Establishing the regulatory framework for drug approval will give context to the conclusion that the US’s biosimilar approval processes is lagging. Biosimilar approval could be streamlined if the FDA utilizes the lessened burden on manufacturing regulation created by the 2017 Amended US-EU MRA. Working towards a similarly structured mutual recognition scheme for biosimilar products is a viable solution for the lagging US biosimilar market.

II. THE REGULATORY FRAMEWORK FOR DRUG APPROVALS

A. Milestones that Empowered the FDA’s Regulatory Role

In response to consumer-protection concerns, Congress passed the Pure Food and Drugs Act in 1906 which created the FDA.⁷ At that time, there was no requirement for regulatory approval of any information before marketing.⁸ The only requirement was for drugs to meet standards of strength and purity, enforced by the Bureau of Chemistry in the Department of Agriculture.⁹ The government had the burden of proof for showing that a drug’s label was false and misleading to take a product off the market.¹⁰

In *U.S. v. Johnson*, the Supreme Court in 1911 ruled that “packages and bottles of medicine bearing labels that stated or implied that the contents were effective in curing cancer” were not misbranded within the meaning of Section 2 of the Food and Drugs Act, even with “the defendant well knowing that such representations were false.”¹¹ This was because the Bureau of Chemistry of the Department of Agriculture¹² only determined whether the ingredients of a product were accurately represented.¹³ They had no power to ascertain a product’s medical

5. See *infra* Part II.C.

6. See *infra* Part III.

7. U.S. FDA, ABOUT FDA, <https://www.fda.gov/AboutFDA/WhatWeDo/History/> (last updated Sept. 29, 2017).

8. MICHELLE MEADOWS, U.S. FDA, PROMOTING SAFE AND EFFECTIVE DRUGS FOR 100 YEARS, <https://www.fda.gov/downloads/AboutFDA/WhatWeDo/History/FOrgsHistory/CDER/UCM586463.pdf> (last updated June 18, 2009)

9. *Id.*

10. *Id.*

11. *U.S. v. Johnson*, 221 U.S. 488 (1911).

12. The Bureau of Chemistry of the Department of Agriculture acted as a proto-FDA before the FDA was established. See MEADOWS, *supra* note 8.

13. *Johnson*, 221 U.S. at 498.

effects.¹⁴ To overcome this hurdle, Congress enacted the Sherley Amendment in 1912 to prohibit labeling medicines with false therapeutic claims intended to defraud purchasers.¹⁵ However, the government still needed to prove an intent to defraud, which limited enforcement power.¹⁶ Finally, Congress passed the Federal Food, Drug, and Cosmetic Act (“FDCA”) of 1938.¹⁷ Under the FDCA, manufacturers now had to demonstrate their drug’s safety in their market approval application to the FDA.¹⁸

Perhaps the most prominent event that effected change in regulatory enforcement was the thalidomide tragedy of the early 1960s. According to Max Sherman and Steven Strauss, “[n]o drug has done, or is likely to do, more toward the strengthening of existing drug laws in various countries and toward the creation of drug laws in others that lacked such legislation before the appearance of this drug in the marketplace.”¹⁹ Thalidomide was a widely used sleeping tablet in Europe.²⁰ It was also used to treat nausea associated with pregnancy.²¹ However, after widespread use adverse events started to trickle in, including “tingling hands, sensory disturbances, and later, motor disturbances and atrophy of the thumb.”²² These adverse events attracted the attention of Dr. Frances Kelsey, a physician and pharmacologist at the FDA.²³ She was concerned about a drug’s effect on pregnancy due to her work with quinine, an anti-malarial drug with teratogenic effects.²⁴ Because she had observed quinine’s adverse effects, she requested more data to show that using thalidomide was safe during pregnancy.²⁵ Her diligence helped America avert a thalidomide-induced birth defect crisis. Across Europe, an alarming number of babies were being born with congenital birth defects.²⁶ Unfortunately, it took years and widespread use to establish the relatedness between

14. *Id.*

15. MEADOWS, *supra* note 8.

16. *Id.*

17. *Id.*

18. *Id.*

19. Max Sherman & Steven Strauss, *Thalidomide: A Twenty-Five Year Perspective*, 31 FOOD DRUG COSM. L.J. 458 (1986).

20. *Id.* at 460.

21. *Id.*

22. *Id.* at 460 (citing Helen B. Taussig, *A Study of the German Outbreak of Phocomelia*, 180 (13) JAMA 1106 (1962)).

23. Sherman, *supra* note 19, at 461.

24. The use of teratogen indicates that a drug has the capacity under certain exposure conditions to produce abnormal development in an embryo or fetus. U.S. FDA, REVIEWER GUIDANCE: EVALUATING THE RISKS OF DRUG EXPOSURE IN HUMAN PREGNANCIES (Apr. 2005), <https://www.fda.gov/downloads/Drugs/Guidances/ucm071645.pdf>.

25. Sherman, *supra* note 19, at 461.

26. *Id.* at 463.

thalidomide and congenital birth defects. Soon, the thalidomide story broke in the US and spurred public discourse on drugs and drug controls.²⁷

Even though it was not approved for use in the US, thalidomide still found its way to hundreds of pregnant women.²⁸ The need for stronger enforcement of FDA regulations resulted in the 1962 Kefauver-Harris Drug Amendments to the Federal FDCA.²⁹ The Investigational New Drug (“IND”) process was born, enacting procedural requirements during clinical investigation.³⁰ Market approval from the FDA was now a requirement.³¹ Manufacturers now had to prove safety and substantial effectiveness for a product’s intended use through well-controlled studies.³² Good manufacturing practices were required and enforced through inspection.³³ Adverse events were required to be reported.³⁴ Further, ethical considerations were implemented: study subjects were required to give informed consent, review boards approved protocols, and ethics committees monitored the risk-benefit of a patient’s participation in a trial.³⁵

Today, the FDA is the global gold standard for rigorous evaluation of safety, quality, and effectiveness before market approval.³⁶ The FDCA³⁷ authorizes the FDA to inspect products already on the market.³⁸ The FDA also regulates manufacturing practices and evaluates new drugs, medical devices and food additives for safety and effectiveness before products are marketed to the public.³⁹ If a product is determined to be unsafe or not FDCA-compliant, the FDA has the power to recall or seize products.⁴⁰ In addition, the FDA issues standards for product

27. *Id.*

28. *Id.*

29. MEADOWS, *supra* note 8.

30. Sherman, *supra* note 19, at 463-64.

31. MEADOWS, *supra* note 8; *see also* 21 U.S.C. § 355(a) (West 2018) (requiring approval of an application for a new drug before introducing it into interstate commerce).

32. MEADOWS, *supra* note 8.

33. 21 U.S.C. § 355(n)(3) (West 2018).

34. 21 U.S.C. § 355(k)(3)(C) (requiring the establishment and maintenance of procedures for reporting data on serious adverse drug experiences).

35. U.S. FDA, INSTITUTIONAL REVIEW BOARDS FREQUENTLY ASKED QUESTIONS, <https://www.fda.gov/RegulatoryInformation/Guidances/ucm126420.htm> (last visited Mar. 29, 2018) [hereinafter INSTITUTIONAL REVIEW BOARDS FAQs].

36. MEADOWS, *supra* note 8.

37. 21 U.S.C. §§ 301-399 (West 2018). Food, Drug and Cosmetic Act (FDCA), Practical Law Glossary Item 7-503-3134.

38. 21 U.S.C. § 341 (West 2018); 21 U.S.C. § 374(a)(1) (West 2018).

39. 21 U.S.C. § 355(a); 21 U.S.C. § 348(b) (West 2018).

40. 21 U.S.C. § 334(a)-(b); 21 U.S.C. § 350(a)-(b) (West 2018); 21 U.S.C. § 360h(e) (West 2018).

labeling and other marketing communications, such as side effects and drug interactions that must be listed on pharmaceutical labels.⁴¹

B. How Do Drugs Get Approved?

Market approval of novel medical therapies weighs two important interests.⁴² First, the product must be safe and effective.⁴³ Second, a thorough but expedient review process determines whether to grant public access to innovative therapies.⁴⁴

A drug manufacturer, also known as the sponsor,⁴⁵ first identifies a medicinal product for commercialization. If the product is a biologic that is also a “drug,” the biologic is subject to additional provisions of the FDCA.⁴⁶ A “biologic,” or “biological product,” refers to a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or protein applicable to the prevention, treatment, or cure of a disease or condition of human beings.⁴⁷

During preclinical development, the sponsor assesses the proposed product’s pharmacological activity and determines if it is reasonably safe for human use.⁴⁸ If so, the sponsor files an Investigational New Drug (“IND”) application.⁴⁹ Clinical trials are then initiated to prove a proposed drug’s safety and efficacy.⁵⁰ Scientifically robust studies produce clinical data that are used to support a drug manufacturer’s application to market the drug, known as a New Drug Application (“NDA”).⁵¹ The NDA also contains proposed labeling, safety updates, drug abuse information, patent information, data from studies outside of the US, institutional review board compliance information, and directions for use.⁵²

41. See 21 U.S.C. §§ 343-343-3, 352, 360 (West 2018).

42. Gail A. Van Norman, *Drugs and Devices: Comparison of European and U.S. Approval Processes*, 1 JACC: BASIC TO TRANSLATIONAL SCI. 399, 400 (2016).

43. *Id.*

44. *Id.*

45. “Sponsor means a person who takes responsibility for and initiates a clinical investigation.” 21 C.F.R. § 312.3 (2017).

46. 42 U.S.C. § 262(j) (2017).

47. 42 U.S.C. § 262(i)(1).

48. U.S. FDA, INVESTIGATIONAL NEW DRUG (IND) APPLICATION, <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm> (last updated Oct. 5, 2017).

49. U.S. FDA, STEP 3: CLINICAL RESEARCH, <https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm> (last updated Jan. 4, 2018).

50. *Id.*

51. *Id.*

52. *Id.*

In the case of biologics, the sponsor submits a Biologics License Application (“BLA”).⁵³ The BLA must include a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product; summaries of results of tests performed on the lot(s) represented by the submitted sample(s); and specimens of the labels, enclosures, and containers.⁵⁴

An FDA review team reviews preclinical and clinical data demonstrating a proposed drug’s safety and efficacy for intended use. After submission, the FDA review team⁵⁵ categorically evaluates the data submitted and conducts clinical site inspections to supplement their review.⁵⁶ A decision to grant approval is made within six to ten months.⁵⁷

1. IND Requirements

The IND application is necessary to commence clinical studies because it is the means through which a sponsor obtains an exemption from the FDA to ship the investigational drug to interstate clinical investigators.⁵⁸ At a minimum, an application must include (1) full reports of investigations that demonstrate a drug’s safety and efficacy in use, (2) a full list of articles used as components of the drug, (3) a full statement of the drug’s composition, (4) a description of the methods used in, the facilities and controls used for, the manufacturing, processing, and packaging of the drug, (5) samples of the drug and articles used as components of the drug, and (6) proposed labeling for the drug.⁵⁹

53. 21 C.F.R. § 601.2(a) (2017).

54. *Id.*

55. A review team consists of specialists representing different scientific fields. A Project Manager coordinates the team’s activities and acts as the primary contact for the sponsor; a medical officer reviews clinical study information; a statistician interprets clinical trial designs and data; a pharmacologist reviews preclinical studies; a pharmacokineticist evaluates a drug’s absorption, distribution, metabolism and excretion processes; and a chemist evaluates a drug’s chemical makeup. STEP 3, *supra* note 49.

56. U.S. FDA, STEP 4: FDA DRUG REVIEW, <https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405570.htm> (last updated Jan. 4, 2018).

57. *Id.*

58. INVESTIGATIONAL NEW DRUG (IND) APPLICATION, *supra* note 48. *See also* 21 U.S.C. § 355(a) (2017) (“No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed...is effective with respect to such drug.”).

59. 21 U.S.C. § 355(b)(1) (2017).

2. *Proving Safety and Efficacy: Clinical Trials of an Investigational New Drug*

An IND application must submit preclinical data from animal pharmacology and toxicology studies to demonstrate a drug's safety and efficacy.⁶⁰ It must also provide detailed protocols for proposed clinical studies.⁶¹

The clinical investigation of a previously untested drug is divided into phases.⁶² In Phase 0 and 1 trials, a small population of healthy subjects are dosed with the investigational product.⁶³ This serves to investigate the pharmacology of the drug in humans, detect side effects associated with increasing doses, and gain early evidence on effectiveness.⁶⁴ These trials establish the product's safety for human use. Phase 2 trials are next. Hundreds of patients who are afflicted with the drug's proposed indication are given incremental doses of the study drug.⁶⁵ This phase will observe the efficacy of the drug for its intended purpose.⁶⁶ Finally, Phase 3 trials increase the patient population.⁶⁷ Up to thousands of patients are dosed with the investigational product to demonstrate efficacy while monitoring adverse reactions.⁶⁸ Afterwards, a risk-benefit profile is developed to inform physician labelling.⁶⁹

a. *Evaluating Safety by Monitoring Adverse Events*

Clinical trial progression is ultimately driven by the adverse events that emerge after using the drug product. An "adverse event" means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.⁷⁰ "Serious adverse events" refer specifically to adverse events with outcomes such as death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability, congenital

60. INVESTIGATIONAL NEW DRUG (IND) APPLICATION, *supra* note 48.

61. U.S. FDA, GUIDANCE FOR INDUSTRY: CONTENT AND FORMAT OF INVESTIGATIONAL NEW DRUG APPLICATIONS (INDS) FOR PHASE 1 STUDIES OF DRUGS, INCLUDING WELL-CHARACTERIZED, THERAPEUTIC, BIOTECHNOLOGY-DERIVED PRODUCTS (Nov. 1995), <https://www.fda.gov/downloads/Drugs/.../Guidances/ucm074980.pdf>.

62. 21 C.F.R. § 312.21 (2017).

63. AM. CANCER SOC'Y, WHAT ARE THE PHASES OF CLINICAL TRIALS?, <https://www.cancer.org/treatment/treatments-and-side-effects/clinical-trials/what-you-need-to-know/phases-of-clinical-trials.html> (last updated Feb. 7, 2017).

64. 21 C.F.R. § 312.21(a)(1).

65. *See* 21 C.F.R. § 312.21(b).

66. 21 C.F.R. § 312.21(b).

67. *See* 21 C.F.R. § 312.21(c).

68. *Id.*

69. *Id.*

70. 21 C.F.R. § 312.32(a).

birth defects, or an important medical event.⁷¹ A serious adverse event is reportable to the FDA in an “IND safety report” when there is a reasonable possibility of a causal relationship between the drug and the adverse event *and* if the event is unexpected.⁷² “Expectedness” refers to whether or not the event is listed in the investigator brochure as an identified risk described in the general investigational plan.⁷³ Such reports must also be made known to participating investigators to whom the sponsor is providing the study drug.⁷⁴

Standardizing causality assessments is trickier. Although causality is ultimately a clinical judgment, there are instances that allude to relatedness: (1) a single occurrence of an event that is uncommon and known to be strongly associated with drug exposure;⁷⁵ (2) one or more occurrences of an event that is not commonly associated with drug exposure, but is other uncommon in the population exposed to the drug;⁷⁶ (3) an aggregate analysis of specific events observed that indicate an event may be occurring more frequently in the drug treatment group than a control group.⁷⁷

The sponsor company and the clinical site monitor the progress of each patient enrolled in the clinical trial.⁷⁸ They do this by selecting qualified investigators, providing them with the information needed to properly conduct the investigative study, monitor the study’s progress, and ensure that the FDA and all participating investigators are promptly informed of significant new adverse events or risk.⁷⁹ Principal investigators lead clinical sites and review adverse events occurring in the clinical trial.⁸⁰ Ultimately, the principal investigator assesses the investigational product’s causality to the adverse event. An Institutional Review Board (“IRB”) reviews clinical protocols before a trial begins, monitors the progress, maintains records, and assure clinical testing meets ethical standards.⁸¹ A Data Monitoring Committee (“DMC”) will review patient data to ensure that a drug is demonstrating safety and

71. *Id.*

72. 21 C.F.R. § 312.32 (c)(1)(i) (2017).

73. *See* 21 C.F.R. §312.21(a).

74. 21 C.F.R. § 312.32(c)(1).

75. 21 C.F.R. § 312.32(c)(1)(i)(A).

76. 21 C.F.R. § 312.32(c)(1)(i)(B).

77. 21 C.F.R. § 312.32(c)(1)(i)(C).

78. U.S. FDA, INVESTIGATOR RESPONSIBILITIES — REGULATION AND CLINICAL TRIALS, (Nov. 13, 2013),

<https://www.fda.gov/downloads/training/clinicalinvestigatortrainingcourse/ucm378565.pdf>.

79. *Id.* at 36.

80. *Id.*

81. INSTITUTIONAL REVIEW BOARDS FAQs, *supra* note 35.

efficacy.⁸² If the patient risk is too high, the trial could be terminated.⁸³ If the drug is not demonstrating efficacy, then it is meaningless to continue the study and deprive patients the standard of care, if available.

b. Proving Efficacy

For marketing approval, companies must present substantial evidence that the investigational product has a clinically meaningful effect.⁸⁴ Patients participate in clinical studies seeking improved survival, detectable benefits such as symptom relief, or decreased chances of developing a disease complication (e.g. stroke).⁸⁵ To show efficacy, clinical trials should have an endpoint with a measurable outcome.⁸⁶ Objective endpoints include quantitative measurements of biochemical parameters, survival, disease exacerbation, or important medical events (e.g. stroke). Subjective measures as endpoints evaluate outcomes such as symptom scores and quality-of-life evaluations.⁸⁷

Ideally, the endpoints will prove efficacy by demonstrating a statistical significance between two treatments or strategies being compared with respect to the endpoint measure.⁸⁸

3. Demonstrating Quality and Potency: Manufacturing Practices

The FDA regulates pharmaceutical quality and manufacturing standards with a series of continuously updated guidance documents published as the Current Good Manufacturing Practice (“CGMP”) Standards.⁸⁹ CGMPs generally outline systems for proper design, monitoring, and control of manufacturing processes and facilities.⁹⁰ This

82. U.S. FDA, ESTABLISHMENT AND OPERATION OF CLINICAL TRIAL DATA MONITORING COMMITTEES FOR CLINICAL TRIAL SPONSORS, <https://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm> (last visited Mar. 29, 2018).

83. *Id.*

84. Eugene J. Sullivan, U.S. FDA, CLINICAL TRIAL ENDPOINTS 3, <https://www.fda.gov/downloads/Training/ClinicalInvestigatorTrainingCourse/UCM337268.pdf> (last visited Jan. 30, 2018).

85. *Id.*

86. See Joseph Spahn, *Clinical Trial Efficacy: What Does it Really Tell You?*, 112 J. OF ALLERGY & CLINICAL IMMUNOLOGY 102 (2003).

87. *Id.*

88. See OFF. OF BEHAV. & SOC. SCI. RES., CLINICAL TRIALS: ENDPOINTS, <http://www.esourceresearch.org/eSourceBook/ClinicalTrials/4Endpoints/tabid/200/Default.aspx> (last visited Jan. 30, 2018).

89. See U.S. FDA, PHARMACEUTICAL QUALITY/MANUFACTURING STANDARDS (CGMP), <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm> (last updated Oct. 6, 2017).

90. U.S. FDA, FACTS ABOUT THE CURRENT GOOD MANUFACTURING PRACTICES (CGMPs),

includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories.⁹¹ Regulation adherence ensures patient safety. Failure to comply with CGMP regulations results in “adulterated products” that could be subject to recall—or in cases of noncompliance with a recall request, an injunction and product seizure.⁹² Information pertaining to the composition, manufacturing, stability, and controls used in drug manufacturing is assessed to ensure that the sponsor can adequately produce and supply consistent batches of the drug.⁹³

C. The EMA’s Regulatory Role

The European Medicines Agency (“EMA”) oversees the European medicines regulatory network through a collaboration between the European Commission (EC) and regulatory authorities in European Economic Area (“EEA”) countries.⁹⁴ Marketing authorization—that is, the legal decision to grant, suspend or revoke a marketing authorization for any medicine—in the EU falls under the purview of the EC.⁹⁵ Market-authorization holders (i.e. biopharmaceutical companies) submit single market-authorization applications for the EMA to evaluate.⁹⁶ In this sense, the EMA’s centralized authorization process is similar in function to the FDA, which oversees all drug approvals in the United States. Under the centralized process, the EMA carries out scientific assessment of the application and recommends approval.⁹⁷ Authorization decisions are made in the interest of public health “on the basis of objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other

<https://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm>
(last updated Oct. 6, 2017).

91. *Id.*

92. *Id.*

93. *Id.*

94. EUROPEAN MED. AGENCY, HISTORY OF THE EMA, http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000628.jsp (last visited Jan. 20, 2018).

95. EUROPEAN MED. AGENCY, WHAT WE DO, http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000091.jsp (last visited Jan. 20, 2018).

96. *See* EUROPEAN MED. AGENCY, LEGAL FRAMEWORK, http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000127.jsp (last visited Jan. 20, 2018).

97. WHAT WE DO, *supra* note 95.

considerations.”⁹⁸ “Every member state of the EU is represented on the EMA committee for Medicinal Products.”⁹⁹

The centralized plan aimed to reduce the cost for drug companies to obtain approvals and eliminate protectionist tendencies of member nations that would otherwise favor domestic products.¹⁰⁰ Moreover, the EMA and Member States cooperate and share expertise in assessing new medicines and safety information through reviewing reported side effects, overseeing of clinical trials, and conducting of manufacturing inspections.¹⁰¹ Functionally, the EMA is a conglomerate of its Member States’ regulatory authorities. As such, the EMA has several routes to drug approval beyond the centralized procedure.

1. EU Authorization through National Authorization

Of course, regulatory authorities of EU Member States can also authorize products nationally. The local regulatory authority would be responsible for authorizing medicines not passing through the centralized procedure.¹⁰² Here, the national regulatory authority would be responsible for verifying that manufacturers and importers of medicinal products coming from outside the EU follow EU-established manufacturing standards.¹⁰³

2. EU Authorization through Mutual Recognition

The EMA is perhaps the “best-established example of regulatory cooperation between medicines authorities.”¹⁰⁴ Within the EMA network, Directive 2004/27/EC outlines a mutual recognition procedure

98. Regulation (EC) 726/2004 of the European Parliament and of the Council: Laying Down Community Procedures for the Authorisation and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Medicines Agency, 2004 O.J. (L 136), 1, 4 https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf [hereinafter Regulation 726/2004/EC].

99. Norman, *supra* note 42.

100. *Id.*

101. EUROPEAN MED. AGENCY, THE EUROPEAN REGULATORY SYSTEM FOR MEDICINES: A CONSISTENT APPROACH TO MEDICINES REGULATION ACROSS THE EUROPEAN UNION, http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2014/08/WC500171674.pdf (last visited Jan. 20, 2018).

102. EUROPEAN MED. AGENCY, NATIONAL COMPETENT AUTHORITIES (HUMAN), http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000155.jsp&mid=WC0b01ac0580036d63 (last visited Jan. 20, 2018).

103. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use, art. 20, 2001 O.J. (L 311).

104. Riccardo Luigetti, Peter Bachmann, Emer Cooke & Tomas Salmonson, *Collaboration, Not Competition: Developing New Reliance Models*, 30 WHO DRUG INFO. 558, 559 (2016).

for EU market authorization.¹⁰⁵ Medicines that already received authorization in one EEA Member State may apply for mutual recognition in other Member States.¹⁰⁶ The applicant will request one Member State to be the “reference Member State” to evaluate the medicine and decide whether to grant authorization.¹⁰⁷ The other Member States, the “concerned Member States,” must adopt a decision that conforms with the approved assessment report from the reference Member State, the summary of product characteristics, and the labelling and package leaflet as approved.¹⁰⁸

3. EU Authorization through the Decentralized Procedure

Directive 2004/27/EC outlines the decentralized procedure for marketing authorization.¹⁰⁹ Though very similar to the mutual recognition procedure, the decentralized procedure is enacted for medicines that have not previously received marketing authorization.¹¹⁰ Like the mutual recognition procedure, it relies on national authorization in one Member State to obtain mutual recognition.¹¹¹ Under the decentralized procedure, identical dossiers are submitted to all Member States where marketing authorization is sought.¹¹² Effectively, this process joins concerned Member States at an earlier stage of evaluation to minimize disagreements when adopting mutual recognition of the novel therapy.

4. Timeline Efficiency Compared to the FDA

The issue is then whether shared expertise framework of the EMA approval process creates any efficiencies. Between 2011 and 2015, the FDA approved 170 new therapeutic agents compared to the EMA which approved 144.¹¹³ The therapeutic areas of the approvals were similar in the two agencies, although the FDA approved more orphan drugs than by the EMA (43.5% vs. 25.0% of the approved agents).¹¹⁴ The total

105. See Directive 2004/27/EC, art. 28, 2004 O.J. (L 136/44).

106. *Id.* at art. 28.

107. *Id.*

108. *Id.*

109. See *id.* at arts. 27-32.

110. EUROPEAN COMM'N, AUTHORISATION PROCEDURES — THE DECENTRALISED PROCEDURE, https://ec.europa.eu/health/authorisation-procedures-decentralised_en (last visited Jan. 20, 2018).

111. *Id.*

112. Directive 2004/27/EC, art. 28, 2004 O.J. (L 136/44).

113. Nicholas S. Downing, Audrey D. Zhang & Joseph S. Ross, *Regulatory Review of New Therapeutic Agents — FDA versus EMA, 2011-2015*, 376 NEW ENG. J. MED. 1386 (2017).

114. *Id.*

review times did vary based on therapeutic areas; the FDA had shorter times for cancer and hematologic disease treatments as well as orphan drugs.¹¹⁵ However, on average FDA review periods were sixty days shorter than those by the EMA.¹¹⁶

D. The Pathway for Approval of Biosimilars in the US and EU

A “biosimilar” is a biological product that is highly similar to a reference product except for minor differences in clinically inactive components.¹¹⁷ In the US, biologic product licensing and regulation is governed by the Public Health Service Act (“PHSA”).¹¹⁸ The Biologics Price Competition and Innovation Act (“BPCIA”) of 2009 passed as part of the Affordable Care Act in 2010.¹¹⁹ The BPCIA created an abbreviated pathway for biosimilar or interchangeable products licensing by relying on the safety and efficacy data in an FDA-approved reference product.¹²⁰ Essentially, BPCIA enables a biosimilar biological product to be licensed based on less than a full complement of product-specific preclinical and clinical data.¹²¹

Genetically engineering cells to produce biologics is a complex process that drives up the costs of biological products.¹²² BPCIA’s aim was to increase access to treatment and to lower health care costs.¹²³ The EU had implemented a similar abbreviated approval pathway for biosimilars in 2005.¹²⁴ Greater availability of biosimilar products, especially in low-income EU countries, influenced national drug

115. *Id.*

116. *Id.*

117. 42 U.S.C. § 262(i)(2)(A).

118. Biological products are approved and regulated under Section 351 of the Public Health Service Act, which is codified at 42 U.S.C. § 262.

119. Darryl Woo, Erin A. Thomson, Janice Ta & Wendy Wang, *Amgen v Sandoz: Marketing Exclusivity Under the BPCIA*, LIFE SCI. INTEL. PROP. REV. (2016).

120. *Id.*

121. LEAH CHRISTL, U.S. FDA, OVERVIEW OF THE REGULATORY FRAMEWORK AND FDA’S GUIDANCE THE DEVELOPMENT AND APPROVAL OF BIOSIMILAR PRODUCTS IN THE US 4, <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM561565.pdf> (last visited Jan. 30, 2018).

122. Practical Law Intellectual Property & Technology, *What You Need to Know About the BPCIA*, Practical Law Legal Update 5-590-4543 (Dec. 2, 2014) (West).

123. *Id.*

124. Martin Schiestl, Markus Zabransky, & Fritz Sörgel, *Ten Years of Biosimilars in Europe: Development and Evolution of the Regulatory Pathways*, 11 DRUG DESIGN, DEV. & THERAPY 1509 (2017).

reimbursement systems.¹²⁵ This resulted in increased access to effective treatment because of reduced costs to patients.¹²⁶

The EU pathway for the approval of biosimilars is comparable to the FDA's process. The Committee for Medicinal Products for Human Use ("CHMP") under the EMA issues guidelines for the biosimilar regulatory framework.¹²⁷ The CHMP provides initial assessments for marketing authorization of new medicines that are ultimately approved centrally by the EMA.¹²⁸

1. Demonstrating Quality of the Proposed Biosimilar

Biosimilars, like all medicinal products approved in the EU and US, must demonstrate pharmaceutical quality.¹²⁹ But unlike traditional pharmaceuticals and their respective generics, biologics are not able to be manufactured as perfect equivalents.¹³⁰ Traditional pharmaceutical drugs are chemically synthesized small molecules.¹³¹ In contrast, biologics are complex macromolecular structures consisting of proteins.¹³² Biologics have inherent variability because they are produced via living cells, which can modify protein structure based on its growth environment.¹³³ However, biologics product quality is not affected so long as the critical attributes of the biologic's structure is carefully monitored and retained.¹³⁴

125. The reimbursement criteria for biosimilars were similar to those for other generic products in that the pricing policies for biosimilar medicines was set in relation to the price of the originator. See Pawl Kawalec et al., *Pricing and Reimbursement of Biosimilars in Central and Eastern European Countries*, 8 FRONTIERS IN PHARMACOLOGY (June 2017), <https://www.frontiersin.org/articles/10.3389/fphar.2017.00288/full>.

126. The high price of original drugs limits access to treatment, especially in low-income Central and Eastern European countries. *Id.*

127. The legal basis for similar biological applications can be found in Regulation 726/2004/EC, O.J. (L 136/1), art. 6.

128. EUROPEAN MED. AGENCY, GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS, CHMP/437/04 (Oct. 30, 2005).

129. EUROPEAN MED. AGENCY, BIOSIMILARS IN THE EU: INFORMATION GUIDE FOR HEALTHCARE PROFESSIONALS 10, http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf (last visited Jan. 30, 2018).

130. U.S. FDA, BIOSIMILAR AND INTERCHANGEABLE PRODUCTS, <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm#biological> (last updated Oct. 23, 2017).

131. BIOTECHNOLOGY INNOVATION ORG., HOW DO DRUGS AND BIOLOGICS DIFFER?, <https://www.bio.org/articles/how-do-drugs-and-biologics-differ> (last visited Apr. 28, 2018).

132. *Id.*

133. Arnold G. Vulto & Orlando A. Jaquez, *The Process Defines the Product: What Really Matters in Biosimilar Design and Production?*, 56 RHEUMATOLOGY iv14 (Aug. 30, 2017).

134. *Id.*

The FDA grants licensure for biosimilars in a process analogous to the aforementioned NDA process.¹³⁵ In the Biologics License Application (“BLA”), the proposed biosimilar must include analytical studies demonstrating that the product is highly similar to the reference product, minus inactive components.¹³⁶ Animal studies are included to assess toxicity.¹³⁷ Clinical studies test safety, purity, and potency of the product for its intended use.¹³⁸ Furthermore, the route of administration, dosage form, and strength of the biosimilar must be same as those of the reference product.¹³⁹ Finally, the manufacturing practices used to produce the biosimilar must meet standards to ensure a safe, pure, and potent product.¹⁴⁰

The FDA, through its Center for Biologics Evaluation and Research (“CBER”),¹⁴¹ “inspects manufacturing plants before it approves products, and thereafter, on a regular basis” to ensure that biological products are conforming to laws and regulations.¹⁴² Companies must report to the CBER within forty-five days of awareness of any biological product deviations from good manufacturing practice that may affect the safety, purity, or potency of a distributed product.¹⁴³ This includes testing, processing, packing, labeling, or storage, or with the holding or distribution of a licensed biological product.¹⁴⁴ Regulatory approvals of biologics are more demanding than regulatory approvals of general drug products. More studies are required to show product quality because of the variability expected in manufacturing biologic products.

2. Comparative Studies to Establish High Similarity and Interchangeability

A biosimilar product must have no clinically meaningful differences between the reference biologic product in terms of safety, purity, and potency of the product.¹⁴⁵ To demonstrate that the active substance of the proposed biosimilar is highly similar to the reference

135. The Food and Drug Administration Modernization Act of 1997 created uniformity between the NDA and BLA approval processes.

136. 42 U.S.C. § 262(k)(2)(A).

137. *Id.*

138. *Id.*

139. *Id.*

140. *Id.*

141. U.S. FDA, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (CBER) RESPONSIBILITIES QUESTIONS AND ANSWERS, <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133072.htm> (last updated Aug. 5, 2015).

142. *Id.*

143. 21 C.F.R. § 606.171 (2017).

144. *Id.*

145. 42 U.S.C. § 262(i)(2)(B).

medicine, comprehensive comparative studies are first conducted with the reference medicine.¹⁴⁶ Extensive biochemical and biophysical analytical methods are used to confirm the primary structure and protein modification that may result from protein biosynthesis.¹⁴⁷ If the proposed biosimilar is structurally comparable to the reference medicine, the positive benefit-risk profile of the reference medicine is conferred upon the biosimilar.¹⁴⁸ The biosimilar can then quickly move through the approval process by relying on the efficacy and safety data of the reference biologic.¹⁴⁹

The next step is to conduct comparative clinical studies in human subjects. “The aim of studies in humans is not to demonstrate safety and efficacy in patients, as these have already been established for the reference medicine.”¹⁵⁰ Rather, the studies ensure that the biosimilar’s pharmacokinetics and pharmacodynamics (describing exposure-response relationships) conforms with the reference product.¹⁵¹

“Interchangeable products” are biosimilars that need to meet additional requirements.¹⁵² As its name suggests, an interchangeable product should be substitutable for the reference product without prescriber involvement; switching back and forth between an interchangeable product and a reference product should not impact the safety nor efficacy.¹⁵³ For interchangeable products, the FDA requires a transition study to show that there are no increases in safety events between a patient cohort that stays on the reference product compared to the cohort that switches to the biosimilar.¹⁵⁴ Though the interchangeability pathway is not required by the FDA, interchangeability is a prerequisite for automatic substitution at the

146. BIOSIMILAR AND INTERCHANGEABLE PRODUCTS, *supra* note 130.

147. Elizabeth Hyland et al., Comparison of the Pharmacokinetics, Safety, and Immunogenicity of MSB11022, a Biosimilar of Adalimumab, with Humira® in Healthy Subjects, 82 BRITISH J. OF CLINICAL PHARMACOLOGY 983 (2016).

148. *Id.*

149. A manufacturer need only show that its biosimilar product is highly similar and has no clinically meaningful differences from the approved reference product (which already has a full profile nonclinical and clinical data). Patient access is much quicker because redundant clinical trials are not necessary. U.S. FDA, BIOSIMILAR DEVELOPMENT, REVIEW, AND APPROVAL, <https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm580429.htm#process> (last updated Oct. 23, 2017).

150. BIOSIMILARS IN THE EU: INFORMATION GUIDE FOR HEALTHCARE PROFESSIONALS, *supra* note 129.

151. CHRISTL, *supra* note 121.

152. BIOSIMILAR AND INTERCHANGEABLE PRODUCTS, *supra* note 130.

153. *Id.*

154. *See id.*

pharmacy level.¹⁵⁵ Pharmacy level interchangeability allows drug substitution without input from a doctor. Pharmacy-level substitution is already the case for traditional generics.¹⁵⁶ To save costs, insurance companies could exclusively cover interchangeable biosimilars when one is available in lieu of paying full price for the original biologic.¹⁵⁷

E. A New Drug is Approved: The Post-Market Landscape

Post-marketing studies allow monitoring of known risks. Furthermore, because the drug is now available to a larger number of patients treated over a longer period, detection of rare adverse drug reactions may be made from the aggregate data. For example, the congenital birth defects linked to thalidomide were not discovered until after mass-market use.¹⁵⁸

Experiences which are both “serious”¹⁵⁹ and “unexpected”¹⁶⁰ must be reported to the FDA within fifteen calendar days.¹⁶¹ All other adverse drug experiences for NDA-approved products are compiled into periodic reports for the FDA quarterly or annually, depending on how long the drug has been approved.¹⁶² Additionally, manufacturers proactively seek information about their products from a variety of sources: scientific literature, commercial marketing experience, epidemiological/surveillance studies.¹⁶³ Failure to establish and maintain records and make reports may result in the FDA withdrawing approval which would prohibit continued marketing of the drug.¹⁶⁴

Since comprehensive clinical testing is often not required, post-market safety monitoring is particularly important for biosimilars because of the limited clinical data available at the time of approval.¹⁶⁵

155. *Id.*

156. Lauren F. Friedman, *An Innovation that Could Transform the Drug Industry Faces a Major Hurdle*, BUS. INSIDER (Apr. 29, 2015), <http://www.businessinsider.com/biosimilars-bioequivalence-and-interchangeability-2015-4>.

157. *Id.*

158. As discussed *supra* Part II.A, thalidomide was widely used across Europe before an alarming number of congenital birth defects were associated with the drug.

159. See 21 C.F.R. § 312.32(a).

160. *Id.*

161. 21 C.F.R. § 314.80(c)(1)(i) (2017).

162. 21 C.F.R. § 314.80(c)(2)(i).

163. 21 C.F.R. § 314.80(b).

164. 21 C.F.R. § 314.80(k).

165. Donna M. Gitter, *Informed by the European Union Experience: What the United States Can Anticipate and Learn from the European Union's Regulatory Approach to Biosimilars*, 41 SETON HALL L. REV. 559, 582-83 (2011).

F. US-EU Harmonization: A Mutual Recognition Agreement

A Mutual Recognition Agreement (“MRA”) is an agreement between two or more countries to recognize a specific process or procedure in the other country.¹⁶⁶ Effectively, MRAs are trade agreements that encourage greater international harmonization of compliance standards and consumer protection.¹⁶⁷ MRAs facilitate market access in an age where the manufacture and distribution of modern medicines is increasingly globalized¹⁶⁸ by strengthening use of each agency’s drug inspection expertise and resources, resulting in “greater efficiencies for both regulatory systems and provide a more practical means to oversee the large number of drug manufacturing facilities outside of the US and EU.”¹⁶⁹

In 1998, the US and EU entered into a MRA with provisions concerning current Good Manufacturing Practices, which were never fully implemented.¹⁷⁰ For the MRA to operate, the US and EU needed “reassurance that the GMP inspectorates on both sides have the capability, capacity and procedures in place to supervise manufacturers of medicines at an equivalent level.”¹⁷¹ As such, since 2014, teams from EU national authorities,¹⁷² the European Commission, EMA, and the FDA have audited and assessed the respective supervisory systems.¹⁷³ Such assessments included internal audits of each country’s processes, workforce skills, compliance with local laws and guidelines.¹⁷⁴

Effective November 2017, US and European regulators agreed on mutual recognition of inspections of medicines conducted in their respective territories.¹⁷⁵ This MRA would allow the US and EU to rely on each other’s good manufacturing practices system, share information

166. U.S. FDA, FREQUENTLY ASKED QUESTIONS / THE MUTUAL RECOGNITION AGREEMENT 1 (July 2017), <https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/UCM544394.pdf> [hereinafter FAQ / THE MUTUAL RECOGNITION AGREEMENT].

167. EUROPEAN MED. AGENCY, MUTUAL RECOGNITION AGREEMENTS, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001843.jsp&mid=WC0b01ac058005f8ac (last visited Jan. 30, 2018) [hereinafter MUTUAL RECOGNITION AGREEMENTS].

168. Luigetti et al., *supra* note 104.

169. FAQ / THE MUTUAL RECOGNITION AGREEMENT, *supra* note 166.

170. *Id.*

171. EU-US MUTUAL RECOGNITION OF INSPECTIONS, *supra* note 1.

172. For a full list of each Member State’s national regulatory authority, see EUROPEAN MED. AGENCY, NATIONAL COMPETENT AUTHORITIES (HUMAN), http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_001155.jsp (last visited Jan. 30, 2018).

173. EU-US MUTUAL RECOGNITION OF INSPECTIONS, *supra* note 1.

174. FAQ / THE MUTUAL RECOGNITION AGREEMENT, *supra* note 166.

175. EU-US MUTUAL RECOGNITION OF INSPECTIONS, *supra* note 1.

on inspections and quality defects, and waive batch testing of products on import.¹⁷⁶ “The 2017 Amended Sectoral Annex to the 1998 US-EU MRA allows the FDA and the EU inspectorates to use inspection reports and other related information obtained during drug manufacturing facility inspections, whether conducted by an EU inspectorate or by the FDA, to help determine whether a facility is manufacturing high quality drugs.”¹⁷⁷

Of note, the MRA stipulates that the FDA will conduct an individual assessment of each EU Member State’s regulatory authority before the MRA is effective.¹⁷⁸ Also, the FDA or EU reserve the ability to require further inspections as deemed necessary.¹⁷⁹

With the enactment of the 2017 Amended US-EU MRA, duplicative inspections should be the exception.¹⁸⁰ This will allow the FDA and EMA to allocate resources toward addressing higher public health risks thereby benefiting patient care.¹⁸¹

176. MUTUAL RECOGNITION AGREEMENTS, *supra* note 167.

177. FAQ / THE MUTUAL RECOGNITION AGREEMENT, *supra* note 166.

178. *Id.*

179. *Id.*

180. *Id.*

181. *Id.*

III. IF BPCIA WAS SUPPOSED TO SPEED THINGS UP, WHY IS BIOSIMILAR APPROVAL STILL SLOW?

A. The United States is Trailing the European Union in Biosimilar Approvals

The first FDA-licensed biosimilar was Zarxio, approved in 2015.¹⁸² In 2016, the FDA only licensed three new biosimilars.¹⁸³ However, 2017 was a banner year for biosimilar approvals by the FDA. The FDA approved five biosimilars in 2017 for a total of nine approved overall.¹⁸⁴ This update may be credited to the FDA's January 2017 release of a long-awaited draft guidance on interchangeability considerations.¹⁸⁵ Previously, the FDA was providing one-on-one advice to sponsors about data expected to demonstrate interchangeability.¹⁸⁶ The draft guidance, "Considerations in Demonstrating Interchangeability With a Reference Product," clarifies expectations.¹⁸⁷ However, the guidance document does recommend that the comparator used in switching studies be a US-licensed reference product instead of a foreign-approved product.¹⁸⁸ Although this guidance is specifically for interchangeable products, it still provides insight into the FDA's standards for biosimilar approval.

The US trails behind the EMA's fifty-four approved biosimilars, which represent sixteen unique biologics.¹⁸⁹ The chart below

182. Sue Sutter, *Biosimilars in 2017: Crowded US FDA Review Queue, Key Legal Decisions*, PINK SHEET PHARMA INTELL. (Jan. 24, 2017), <https://pink.pharmaintelligence.informa.com/PS119882/Biosimilars-In-2017-Crowded-US-FDA-Review-Queue-Key-Legal-Decisions>; U.S. FDA, BIOSIMILAR PRODUCT INFORMATION, <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580432.htm>.

183. *Id.*

184. Jacob F. Siegel & Irena Royzman, *US Biosimilar Approvals Soar in 2017*, BIOLOGICS BLOG (Dec. 18, 2017), <https://www.biologicsblog.com/us-biosimilar-approvals-soar-in-2017>.

185. The draft guidance formally lays out FDA expectations for interchangeability. This has standardized the process which previously relied on one-on-one communications between the agency and sponsor. Sutter, *supra* note 182.

186. Sutter, *supra* note 182.

187. See U.S. FDA, DRAFT GUIDANCE FOR INDUSTRY: CONSIDERATIONS IN DEMONSTRATING INTERCHANGEABILITY WITH A REFERENCE PRODUCT, (Jan. 2017), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf>.

188. *Id.* at 15. See also *infra* Part V.C for discussion on how this requirement could be superseded by the EU-US Mutual Agreement.

189. As of Dec. 30, 2018 there are fifty-three approved biosimilars and one approval pending. See EUROPEAN MED. AGENCY, LIST OF BIOSIMILARS APPROVED BY THE EMA, <http://www.ema.europa.eu/ema/> (select "Search" under "Medicines" tab; then select "Human" category; then select "Biosimilars" under medicine type) (last visited Dec. 30, 2018) [hereinafter LIST OF BIOSIMILARS APPROVED BY THE EMA].

demonstrates that the EU has a wide breadth of available biosimilars. For some active substances, the EU has approved multiple biosimilars.

Table 1: Number of Biosimilars Approved in the EMA v. FDA

Active Substance	Brand Name ¹⁹⁰	# Approved by EMA ¹⁹¹	# Approved by FDA ¹⁹²
adalimumab	Humira [®]	8	3
bevacizumab	Avastin [®]	1	1
enoxaparin sodium	Lovenox [®]	2	0
epoetin alfa	Epogen [®]	3	1
epoetin zeta	Retacrit [®]	2	0
etanercept	Enbrel [®]	2	1
filgrastim	Neupogen [®]	7	2
follitropin alfa	Gonal-f [®]	2	0
infliximab	Remicade [®]	4	3
insulin glargine	Lantus [®]	3	0
insulin lispro	Humalog [®]	1	0
pegfilgrastim	Neulasta [®]	5	2
rituximab	Rituxan [®]	6	1
somatropin	Norditropin [®]	1	0
teriparatide	Forteo [®]	2	0
trastuzumab	Herceptin [®]	4	2
	TOTAL	53	16

The FDA and EMA have nine approved biosimilars in common.¹⁹³ Three biosimilars are exclusively approved in the US; Ixifi (infliximab),

190. To identify brand name from active substance, see *Drugs A-Z List*, RXLIST, https://www.rxlist.com/drugs/alpha_a.htm (last visited Nov. 3, 2018).

191. LIST OF BIOSIMILARS APPROVED BY THE EMA, *supra* note 189.

192. U.S. FDA, BIOSIMILAR PRODUCT INFORMATION, <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580432.htm>.

193. The nine approved biosimilars in common are: Amgevita (adalimumab), Cyltezo (adalimumab), Hyrimoz (adalimumab), Mvasi (bevacizumab), Retacrit (epoetin alfa), Erelzi (etanercept), Zarzio (filgrastim), Nivestym (filgrastim), and Inflectra (infliximab)). *Compare*

Renflexis (infliximab), and Ogivri (trastuzumab) are not yet approved by the EMA as of December 2018. However, for each of these, at least one biosimilar with the same active substance is authorized for sale in the EU market. Seven active substances approved in the EMA have not yet been approved by the FDA.

Table 2 below shows that the EMA has been approving biosimilars for over a decade, the first approved in 2006. In contrast, the first FDA-approved biosimilar was in 2015.¹⁹⁴ The EMA approval dates also show that the EMA approves more biosimilars every year.¹⁹⁵ The FDA is also increasing its approval rate, though with only three years' worth of data—and pending patent litigation and comments on the FDA's released interchangeability guidance document—it is difficult to determine if this approval trend will continue.¹⁹⁶

Table 2: Biosimilar Approval Dates in the EMA v. FDA

Active Substance	Brand Name ¹⁹⁷	Biosimilar Name	EMA Approved ¹⁹⁸	FDA Approved ¹⁹⁹
adalimumab	Humira [®]	Amgevita	Mar-2017	Sep-2016
		Cyltezo	Nov-2017	Aug-2017
		Halimatoz	Jul-2018	-
		Hefiya	Jul-2018	-
		Hulio	Sep-2018	-
		Hyrimoz	Jul-2018	Oct-2018
		Imraldi	Aug-2017	-
		Solymbic	Mar-2017	-
bevacizumab	Avastin [®]	Mvasi	Jan-2018	Sep-2017
	Lovenox [®]	Inhixa	Sep-2016	-

LIST OF BIOSIMILARS APPROVED BY THE EMA, *supra* note 189 with BIOSIMILAR PRODUCT INFORMATION, *supra* note 182.

194. Sandoz's Zarxio is the first biosimilar to be approved and commercialized in the U.S. See Siegel & Royzman, *supra* note 184 and BIOSIMILAR PRODUCT INFORMATION, *supra* note 182.

195. One in 2006, five in 2007, two in 2008, two in 2009, one in 2010, four in 2013, three in 2014, four in 2016, sixteen in 2017, and fifteen in 2018. See *supra* Table 2.

196. Five of nine biosimilars approved in the U.S. were approved in 2017. See *infra* Table 2.

197. To identify brand name from active substance, see *Drugs A-Z List*, RXLIST, https://www.rxlist.com/drugs/alpha_a.htm (last visited Nov. 3, 2018).

198. LIST OF BIOSIMILARS APPROVED BY THE EMA, *supra* note 189.

199. BIOSIMILAR PRODUCT INFORMATION, *supra* note 182.

Active Substance	Brand Name ¹⁹⁷	Biosimilar Name	EMA Approved ¹⁹⁸	FDA Approved ¹⁹⁹
enoxaparin sodium		Thorinane	Sep-2016	-
epoetin alfa	Epogen [®]	Abseamed	Aug-2007	-
		Binocrit	Aug-2007	-
		Epoetin Alfa Hexal	Aug-2007	-
		Retacrit	Dec-2007	May-2018
		Silapo	Dec-2007	-
etanercept	Enbrel [®]	Benepali	Jan-2016	-
		Erelzi	Jun-2017	Aug-2016
filgrastim	Neupogen [®]	Accofil	Sep-2014	-
		Filgrastim Hexal	Feb-2009	-
		Grastofil	Oct-2013	-
		Nivestim	Jun-2010	Jul-2018
		Ratiograstim	Sep-2008	-
		Tevagrastim	Sep-2008	-
		Zarzio	Feb-2009	Mar-2015
follitropin alfa	Gonal-f [®]	Bemfola	Mar-2014	-
		Ovaleap	Sep-2013	-
infliximab	Remicade [®]	Flixabi	May-2016	-
		Inflectra	Sep-2013	Apr-2016
		Ixifi	-	Dec-2017
		Remsima	Sep-2013	-
		Renflexis	-	May-2017
		Zessly	May-2018	-
insulin glargine	Lantus [®]	Abasaglar (previously Abasria)	Sep-2014	-

Active Substance	Brand Name ¹⁹⁷	Biosimilar Name	EMA Approved ¹⁹⁸	FDA Approved ¹⁹⁹
		Lusduna	Jan-2017	-
		Semglee	Mar-2018	-
insulin lispro	Humalog [®]	Insulin lispro Sanofi	Jul-2017	-
		Fulphila	Nov-2018	Jun-2018
		Pelgraz	Sep-2018	-
pegfilgrastim	Heulasta [®]	Pelmeg	Nov-2018	-
		Udenyca	Sep-2018	Nov-2018
		Ziextenzo	Sep-2018	-
		Blitzima	Jul-2017	-
		Ritemvia	Jul-2017	-
		Rituzena (previously Tuxella)	Jul-2017	-
rituximab	Rituxan [®]	Rixathon	Jun-2017	-
		Riximyo	Jun-2017	-
		Truxima	Feb-2017	Nov-2018
somatropin	Norditropin [®]	Omnitrope	Apr-2006	-
		Movymia	Jan-2017	-
teriparatide	Forteo [®]	Terrosa	Jan-2017	-
		Herzuma	Feb-2018	Dec-2018
		Kanjinti	May-2018	-
		Ogivri	-	Dec-2017
		Ontruzant	Nov-2017	-
		Trazimera	Jul-2018	-
trastuzumab	Herceptin [®]			

IV. AN ANALYSIS OF WHAT IS SLOWING THE UNITED STATES DOWN

Of note, all currently approved biosimilars in the EU have approved reference biologics that are approved in the US.²⁰⁰ Since the reference product has already been approved, the issue is not the safety and efficacy profile of the biologic itself. There is a delay in US approval of biosimilars, even though the reference products are long-established. The discrepancies between the number of biosimilars approved by the FDA versus by the EMA can be explained in a few ways.

A. Differences Between the EMA and FDA Biosimilar Approval Pathways

First, the EMA has a few more years of experience approving biosimilars, as their abbreviated pathway has been in place since 2005.²⁰¹ Though the EMA is more seasoned in the biosimilar field, their methods of review do not differ much from that of the FDA.²⁰² Furthermore, the FDA on average has a shorter review time for marketing authorization than the EMA.²⁰³ Additionally, biosimilars should have a lower rigor of review than original BLAs because they can ride on the coattails of the reference product's safety and efficacy data. Therefore, the delay is not due to protracted FDA review timelines.

For the Center for Biologics Evaluation and Research ("CBER"),²⁰⁴ the only area of focused review is manufacturing practices, product quality, and interchangeability. Herein lies one difference between the EU and US biosimilar approval process: the FDA pathway offers a regulatory designation for interchangeability.²⁰⁵ The EMA, essentially a network of the regulatory bodies of its Member States, allows

200. Reference biologics can be looked up by brand name on the FDA website. See U.S. FDA, DRUGS@FDA: FDA APPROVED DRUG PRODUCTS, <https://www.accessdata.fda.gov/scripts/cder/daf/>.

201. Schiestl et al., *supra* note 124.

202. *Id.* Europe, the USA, and Japan adhere to the International Conference on Harmonization Q5E tripartite comparability guidelines. See EUROPEAN MED. AGENCY, ICH TOPIC Q5E: COMPARABILITY OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS, (June 2005), http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002805.pdf (which outlines considerations for comparability exercises, quality, manufacturing process, comparability during development, and nonclinical and clinical studies).

203. Norman, *supra* note 42.

204. The Center for Biologics Evaluation and Research (CBER) "ensure[s] the safety, purity, potency, and effectiveness of biological products including vaccines, blood and blood products, and cells, tissues, and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury." U.S. FDA, CBER VISION & MISSION, <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm122878.htm>.

205. 42 U.S.C. § 262(k)(4)(B).

individual members to adopt the heightened interchangeability requirement at the national level.²⁰⁶

Pursuing interchangeability may be worth adding a transition study, but an additional study does increase the approval timelines. Interchangeability standards are clearer compared to formulary rules for switching patients to “highly similar” biosimilars.²⁰⁷ Theoretically, this means that the United States has a longer process for biosimilar regulatory approval if there is an incentive to pursue interchangeability *before* approval to engender trust by patients and clinicians for substitution. In comparison, the heightened interchangeability requirement is incidental in the EMA.²⁰⁸ EU Member States individually regulate interchangeability, switching, and substitution.²⁰⁹ Of course, information from scientific evaluation performed by EMA’s scientific committees can be used to support decisions.²¹⁰ Nevertheless, the member-state level approval does not affect EMA biosimilar approval. The impact is downstream, *after* a biosimilar is already approved. The impact is at the prescription and pharmacy-level, where each member-state has regulations on how a biosimilar may be used and its insurance reimbursement scheme.²¹¹

B. Unfamiliarity with Biosimilars

Despite the licensure pathway for biosimilars in the US, the biosimilar approvals may be slow because of the lack of statutory guidance, the higher hurdles of entry as compared to generic products, and a general lack of familiarity with biosimilar products.²¹² Surveyed US health care professions expressed safety concerns and the need for more evidence before considering biosimilars as acceptable alternatives.²¹³ Since FDA biosimilar approval is based on molecular similarity, the lessened emphasis on clinical evidence from randomized

206. Schiestl et al., *supra* note 124.

207. See Stephen Barlas, *FDA Guidance on Biosimilar Interchangeability Elicits Diverse Views*, 42 PHARMACY & THERAPEUTICS 509 (2017).

208. EUROPEAN MED. AGENCY, BIOSIMILARS IN THE EU: INFORMATION GUIDE FOR HEALTHCARE PROFESSIONALS 29, http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf (last visited Jan. 30, 2018).

209. *Id.*

210. *Id.*

211. Evelien Moorkens et al., *Policies for Biosimilar Uptake in Europe: An Overview*, PLOS ONE (Dec. 28, 2017), <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0190147>.

212. Ralph Boccia et al., *Can Biosimilars Help Achieve the Goals of US Health Care Reform?*, 9 CANCER MGMT. & RES. 197 (June 1, 2017), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5459961/>.

213. *Id.*

trials raises concerns about immunologic effects, especially if a prescriber were to switch a patient from the standard of care to a biosimilar.²¹⁴ Approved interchangeable products could alleviate these concerns. However, no biosimilar has yet been designated as interchangeable in the US.²¹⁵

C. Patent Rights Affecting Approval Timelines

Patent litigation could also be slowing down the FDA process. Companies can market approved biosimilars after the reference medicine market protection expires after about ten years.²¹⁶ As of 2017, thirty-seven biosimilars are approved by the EMA. In the US, biosimilars will not be approved until twelve years after the date a reference product was first licensed.²¹⁷

In 2015, the Supreme Court by unanimous decision in *Sandoz v. Amgen* paved the way for the first biosimilar approval in the US.²¹⁸ Sandoz produced Zarxio (filgrastim) with the intention of marketing Zarxio with Amgen's Neupogen as the reference product, in accordance to the BPCIA.²¹⁹ The FDA accepted Sandoz's application for review. Sandoz then gave notice to Amgen of its intent to market Zarxio immediately upon FDA approval.²²⁰ Blindsided, Amgen sued Sandoz for violations of the BPCIA, which included Sandoz's failure to provide notice of commercial marketing under § 262(l)(8)(A) prior to obtaining licensure from the FDA.²²¹ "Section 262(l) (8)(A) contains a single timing requirement: The applicant must provide notice at least 180 days prior to marketing its biosimilar."²²² There is no reference in the applicable statute to a notification timing requirement prior to FDA licensure. By not creating an artificial marketing delay for approved biosimilars, the Court created a profit motive for biosimilar marketers. In theory, *Sandoz* should expedite the timelines for biosimilars to hit the market, but the effects remain yet to be seen.

214. *Id.*

215. Joshua Cohen, *What's Holding Back Market Uptake of Biosimilars?*, FORBES, June 29, 2018, <https://www.forbes.com/sites/joshuacohen/2018/06/20/whats-holding-back-market-uptake-of-biosimilars/#12f060f9691a>.

216. EUROPEAN MED. AGENCY, BIOSIMILARS IN THE EU: INFORMATION GUIDE FOR HEALTHCARE PROFESSIONALS 28 (2017), https://www.ema.europa.eu/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf.

217. 42 U.S.C. § 262(k)(7)(A).

218. *See Sandoz Inc. v. Amgen Inc.*, 137 S. Ct. 1664 (2017).

219. *Id.* at 1666.

220. *Id.*

221. *Id.* at 1667.

222. *Id.* at 1677.

Notably, like the EU regulatory scheme, the BPCIA does not allow a sponsor to renew data exclusivity due to changes in drug strength, formulation, or route of administration.²²³ This is to prevent arbitrary formulary changes that act as a pretext for extending the data exclusivity period. However, the BPCIA does allow for “second-generation biological product with structural modifications” that changes the safety, purity, or potency of the original product.²²⁴ Such restrictions on a sponsor’s data exclusivity should promote biosimilars approval.

D. A Case Study: The FDA Rejects Pfizer’s Epoetin Biosimilar

Epoetin alfa is an injectable drug that treats anemia associated with chronic kidney failure, including patients that are receiving dialysis.²²⁵ It works by stimulating the bone marrow to produce red blood cells. It is a treatment, not a cure, and is used indefinitely.²²⁶

In an FDA Briefing Document posted May 25, 2017 prior to an advisory committee meeting, FDA reviewers lauded Pfizer’s epoetin alfa biosimilar “Epoetin Hospira” as being “highly similar” to Amgen’s Epogen based on the totality of analytical data.²²⁷ Surprisingly, despite the endorsement from the FDA staff and an advisory committee, Pfizer’s biosimilar for Amgen’s Epogen was rejected a second time.²²⁸ The crux of the issue was a fill-finish plant that was acquired by Pfizer with their acquisition of Hospira.²²⁹ The BLA listed this plant as a potential manufacturing site for the proposed biosimilar,²³⁰ although it was subject to four warning letters in a four year period.²³¹ Other manufacturing sites within the same network were cited for CGMP violations too.²³² This

223. Gitter, *supra* note 165, at 591.

224. *Id.*

225. Omudhome Ogburu, *Epoetin Alfa*, MEDICINENET.COM, https://www.medicinenet.com/epoetin_alfa/article.htm#what_is_the_dosage_for_epoetin_alfa? (last visited Jan. 30, 2018).

226. *Id.*

227. U.S. FDA, FDA BRIEFING DOCUMENT, ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING, BLA 125545 “EPOETIN HOSPIRA,” A PROPOSED BIOSIMILAR TO EPOGEN/PROCRIT (EPOETIN ALFA) (May 25, 2017), <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM559967.pdf>.

228. Eric Palmer, *FDA Rejects Pfizer’s Epogen Biosimilar for the Second Time*, FIERCEPHARMA (June 22, 2017), <https://www.fiercepharma.com/regulatory/fda-rejects-pfizer-s-epogen-biosimilar-for-a-second-time>.

229. *Id.*

230. Press Release, Pfizer, Pfizer Provides Update on Proposed Epoetin Alfa Biosimilar (June 22, 2017), <https://investors.pfizer.com/investor-news/press-release-details/2017/Pfizer-Provides-Update-on-Proposed-Epoetin-Alfa-Biosimilar/default.aspx>.

231. Palmer, *supra* note 228.

232. Andrew D. Cohen, *The Travails of the First U.S. EPO Biosimilar*, BIOLOGICS BLOG (July 10, 2017), <https://www.biologicsblog.com/the-travails-of-the-first-u-s-epo-biosimilar>.

unexpected rejection is expected to delay Epoetin Hospira through 2018.²³³ In contrast, Binocrit, the first epoetin alfa biosimilar, was approved by the EMA in 2007, over ten years ago.²³⁴

Since Binocrit was approved over a decade ago, it does not seem that there are misgivings about the safety and efficacy of the product itself. The variable affecting its rejection was manufacturing practices that were not compliant with relevant regulation. This surprising rejection illustrates that manufacturing fidelity is a key component to biosimilar approval. Now, with the US mutually recognizing EU-approved manufacturing sites as compliant, perhaps there is a way for the US to accept the biosimilars that are produced at those sites.

V. EU-APPROVED BIOSIMILARS COULD PAVE THE WAY FOR APPROVALS IN THE UNITED STATES

A. Mutual Recognition of Manufacturing Inspections Does Make Mutual Recognition of Biosimilars Feasible

One justification for the 2017 Amendment to the US-EU MRA was to better allocate resources for the benefit of patient safety and public health.²³⁵ The MRA aimed to reduce duplicative work while still recognizing the FDA and EU's regulatory autonomy by keeping the door open to inspections as needed.²³⁶

The FDA could easily take advantage of this new efficiency. In the case of epoetin alpha above, the FDA could grant access to epoetin alfa biosimilars already approved in the EMA. Given that the bottleneck of the biosimilar approval process is manufacturing assurances, accepting existing data from the EMA will expedite the FDA review process. Biosimilars that reference a biologic that has been on the market for a long time should face no obstacle in terms of patent rights. Furthermore, biosimilars that have been on the European market for years should have fewer quality, efficacy, and safety concerns because it has the benefit of post-market monitoring.²³⁷ If the MRA could be applied to biosimilar review and approval, the US would be a step closer to a more competitive and affordable biologics market.

233. *Id.*

234. LIST OF BIOSIMILARS APPROVED BY THE EMA, *supra* note 189.

235. FAQ / THE MUTUAL RECOGNITION AGREEMENT, *supra* note 166.

236. *Id.*

237. As discussed in *supra* Part II.E, post-market drug use by a larger patient population will yield aggregate epidemiological data that may not have been observed during a clinical trial's limited time period and scope.

B. Some Countries Already Mutually Recognize Third-Party Data for Assessment Purposes...

Mutual recognition of assessment and inspection results is not a novel concept. There are non-EU regulatory authorities that base their market approvals on EU assessments.²³⁸ Switzerland, for example, will make a medicinal product already authorized in another country readily available to its patient population as rapidly as possible.²³⁹ This has reduced new product review time by up to twenty percent.²⁴⁰ This example highlights a generous application of the mutual recognition doctrine. Admittedly, Switzerland's deference to a mutual recognition regulatory standard is colored by Switzerland's special relationship with the EU. Like EU-member countries, the Swiss-EU relationship is motivated by economic protectionism.²⁴¹ The US does not have such a relationship with the EU. Thus, a mutual recognition model like Switzerland's is too deferential to EMA authority to be a possibility in the US.

Perhaps a more conservative model is the International Generic Drug Regulators Programme ("IGDRP"),²⁴² which launched an information-sharing pilot in 2014 to enable mutual recognition of generic drugs across participating countries.²⁴³ In addition to the EU authorities, participants include regulatory authorities for Canada (Health Canada), Switzerland (Swissmedic), Taiwan (Taiwan Food and Drug Administration), and Australia (Therapeutic Goods Administration).²⁴⁴ IGDRP utilized the EU decentralized procedure to model their initiative.²⁴⁵ As discussed above, under the decentralized procedure Member States adopt mutual recognition of medicines that have not previously received marketing authorization by relying on the national authorization granted by one Member State.²⁴⁶ Here, the participating members agreed to converge their regulatory standards so that drugs approved in one participating country has a pathway for

238. Luigetti et al., *supra* note 104, at 562.

239. *Id.* at 563.

240. *Id.*

241. Switzerland's economic and trade relations with the EU are governed through a series of bilateral agreements, which grants Switzerland access to the EU's single market. The EU is Switzerland's main trading partner. See EUROPEAN COMM'N, COUNTRIES AND REGIONS: SWITZERLAND, <http://ec.europa.eu/trade/policy/countries-and-regions/countries/switzerland/> (last updated Apr. 16, 2018).

242. International Generic Drug Regulators Programme was launched to increase efficiency in generic drug review.

243. Luigetti et al., *supra* note 104, at 561.

244. *Id.*

245. Directive 2004/27/EC outlines the decentralized procedure for marketing authorization. See Directive 2004/27/EC, O.J. (L 136/44), art. 24.

246. Procedure discussed *supra* Part II.B.3.

authorization in another country without duplicating effort.²⁴⁷ The program stated that promoting generic drug availability was a goal, even though the program excluded biosimilars.²⁴⁸ However, because biosimilars are analogous to generics—they are reproductions of an approved reference product with an established safety and efficacy record—recognition of biosimilars among IGDRP participants could follow the same procedure. Likewise, the US could also participate in such a program. However, because the FDA was founded upon consumer protection principles (as opposed to the EMA's economic protection principles),²⁴⁹ basing approvals off other countries' evaluations sacrifices too much regulatory authority. This is a huge jump from merely accepting multinational data as a supplement to an approval.

The FDA will use, where appropriate, foreign reviews to supplement its evaluation of a product for market authorization.²⁵⁰ As clinical research is becoming increasingly global the FDA recognizes that sponsors may conduct multinational clinical studies.²⁵¹ When the foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with the requirements in 21 C.F.R. § 312.120²⁵² for the data to qualify for marketing approval.²⁵³ The study must produce data that can be validated by the FDA and study sites must be open to onsite inspection if necessary.²⁵⁴

247. Mike Ward, *Regulatory Harmonization*, 28 WHO DRUG INFO. 3, 5-6 (2014), http://www.who.int/medicines/publications/druginformation/DI_28-1_Regulatory-Harmonization.pdf.

248. *Id.* at 6.

249. Historically, the FDA was empowered by consumer-protection concerns, as discussed *supra* Part II.A. The EMA, as the EU's regulatory agency, promotes an EU's principle to achieve market efficiency via a single market. *See* EUROPEAN MED. AGENCY, FACT SHEETS ON THE EUROPEAN UNION: MEDICINES AND MEDICAL DEVICES, <http://www.europarl.europa.eu/factsheets/en/sheet/46/consumer-policy-principles-and-instruments>.

250. Luigetti et al., *supra* note 104, at 563.

251. U.S. FDA, GUIDANCE FOR INDUSTRY AND FDA STAFF: FDA ACCEPTANCE OF FOREIGN CLINICAL STUDIES NOT CONDUCTED UNDER AN IND FREQUENTLY ASKED QUESTIONS 2 (Mar. 2012), <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf>.

252. 21 C.F.R. § 312.120 governs foreign clinical studies not conducted under an IND. Under this section, studies are acceptable if they were conducted in compliance with good clinical practice, which is also defined in the section. The produced data must also be able to be validated by the FDA.

253. 21 C.F.R. § 312.120.

254. *Id.*

C. ...But the FDA Indicates that Interchangeability Comparators Should be US-Approved

Accepting multinational clinical data as a supplement to a marketing approval application still allows the FDA to retain regulatory autonomy. The FDA could also accept supplemental clinical data for proposed biosimilars. In comparison, the EMA accepts data for biosimilars that were compared with foreign-approved biologics as long as there are bridging studies that compare the foreign-approved biologic with the locally licensed version.²⁵⁵ To an extent, the FDA will accept comparison study data for highly similar biologics, but the FDA stops short of allowing foreign comparator products to be used to demonstrate interchangeability.²⁵⁶ As discussed above, interchangeability is effectively mandatory in the US market.²⁵⁷

In January 2017, the FDA published the long-awaited draft guidance for industry titled “Considerations in Demonstrating Interchangeability With a Reference Product.”²⁵⁸ Of note, the draft guidance document states that a non-US-licensed comparator may be used for purposes of demonstrating biosimilarity, but “using a non-US-licensed comparator product generally would not be appropriate” in a switching study supporting a determination of interchangeability.²⁵⁹ Switching studies are designed to assess whether switching between a comparator and the proposed biosimilar will affect the immune system’s response once the switch occurs.²⁶⁰ A non-US-licensed comparator product could have subtle differences with a US-licensed comparator product.²⁶¹ Results from a switching study using a non-US-licensed comparator product would lead to uncertainty about the cause of any immunologic responses.²⁶²

However, the US-licensed comparator requirement does not detract from the US-EU MRA’s potential to give EU-approved biosimilars a pathway for US approval, even under heightened interchangeability

255. Christopher J. Webster & Gillian R. Woollett, *A ‘Global Reference’ Comparator for Biosimilar Development*, 31 *BIODRUGS* 279, 279 (May 19, 2017), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5541093/pdf/40259_2017_Article_227.pdf.

256. *Id.*

257. *See supra* note 148 and accompanying text. Biosimilars can only be substituted for a prescribed biologic if it is interchangeable. *See* BIOSIMILAR AND INTERCHANGEABLE PRODUCTS, *supra* note 130.

258. U.S. FDA, DRAFT GUIDANCE FOR INDUSTRY: CONSIDERATIONS IN DEMONSTRATING INTERCHANGEABILITY WITH A REFERENCE PRODUCT (Jan. 2017), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf>.

259. *Id.* at 15.

260. *Id.*

261. *Id.*

262. *Id.*

requirements. All the EMA-approved biosimilars have US-approved biologic reference products.²⁶³ EMA-approved biosimilars that were approved based on comparator studies with a US-approved biologic reference product can still qualify under the FDA draft guidance. In that scenario, switching studies meeting the FDA criteria have already been completed, albeit in another country.

D. Complete Mutual Recognition of Approved Products is Likely Not Realistic...

Complete mutual recognition of approved products has been proposed as clinical development of novel therapies become increasingly globalized. However, the legal frameworks of each Member State of the EMA and the FDA are too much to untangle anytime soon.²⁶⁴ The healthcare systems are so vastly different, meaning that there are differing levels of motivations to use biosimilars as a medicine price control scheme. The EU, with a more socialized healthcare approach, is incentivized to drive down the costs of therapeutic products, sometimes by implementing government-set prices in order to achieve that objective.²⁶⁵ For the US, the BPCIA as part of the Affordable Care Act is slowly driving the US towards approving more biosimilars. But the biosimilar approval pathway shows a uniquely American concern for patent rights: developers are granted twelve years of market exclusivity for new biologics, but future access to these high cost drugs is encouraged by allowing entrants to compete after exclusivity and patent expiration.²⁶⁶

Ultimately, the discrepancy in the approach to biosimilars is because the FDA and EMA were founded on different principles. The FDA originated as a consumer protection agency.²⁶⁷ The EMA was born from the EU as a market protection initiative.²⁶⁸ Different origin stories do inform their respective openness to mutual recognition procedures: the FDA has a tradition of autonomy and a long-history of increasingly discerning scientific standards, which could mean that it is wary of trusting other agencies, even the EMA, to do its work. In contrast, the EMA has a tradition of fostering collaboration amongst its country

263. See *supra* Part III.A, Table 2.

264. Luigetti et al., *supra* note 104, at 565.

265. Carmen Paun, *Europe's Health Systems on Life Support*, POLITICO, <https://www.politico.eu/article/europe-health-care-systems-on-life-support-special-report-drug-pricing-medicines-public-services/> (last updated Oct. 7, 2016).

266. Joseph P. Fuhr et al., *Product Naming, Pricing, and Market Uptake of Biosimilars*, 4 GENERICS & BIOSIMILARS INITIATIVE J. 64 (2015).

267. See *supra* Part II.

268. See *supra* Part II.C.

participants, meaning it was built on mutual recognition procedures between Member States of the EU and other countries in the European Economic Area.

E. ...But Biosimilars are a Good Start towards International Harmonization

Variation in the biologics manufacturing processes exist for reasons such as “scaling up of the process, improving efficiency, or modernization when equipment needs to be updated or replaced.”²⁶⁹ “To allow such manufacturing changes to occur without the need for companies to conduct a new clinical development program, regulators devised the comparability concept to establish whether the pre- and postchange [sic] products were sufficiently similar to permit ongoing marketing under the same product label.”²⁷⁰ As such, with the step that the FDA and EMA have now taken to align their manufacturing standards, any misgivings that the FDA may have to an EMA-approved biosimilar can be resolved via the comparability scheme.

A change to the manufacturing process must always be approved by regulators. Analytical and functional data is usually sufficient for continued approval of the biosimilar. In rare cases, additional clinical studies need be done to demonstrate no impact on quality, safety, and efficacy.²⁷¹ Here, it logically follows that the FDA could move towards developing a means to grant authorization to a requesting manufacturer that is already producing an EMA-approved biosimilar. Any concerns about the safety and efficacy of the EMA-approved biosimilar can be addressed by invoking the right to conduct supplementary inspections, a right reserved in the 2017 Amended US-EU MRA.

VI. CONCLUSION

Instead of being years behind, the United States’ biosimilars initiative could be ramped up so that the market for biosimilars in the United States is comparable to the European Union’s. The FDA releasing a formal guidance on interchangeability requirements certainly will clear some regulatory uncertainty in the US. Additionally, the Mutual Recognition Agreement for manufacturing inspections presents a great opportunity for the FDA to approve a wider range of biosimilars whose manufacturing practices are deemed compliant by the EU. After the United States validates EU manufacturing sites on a national

269. Schiestl et al., *supra* note 124.

270. *Id.*

271. *Id.*

member-state level, the US could approve biosimilars produced at those approved sites.

The next step is for the FDA to build upon the agreement and work towards recognizing that the biosimilars that are manufactured under robust EMA guidelines are fit for approval in the United States too. By approving more biosimilars in the US, competition increases in the biologics market, which will drive down drug costs, which is analogous to the effect that generic product availability has on drug pricing. This is important because biologics are prone to price markup. Unlike traditional drugs, biologics are genetically engineered from cell cultures, which do make them costlier to produce. Additionally, biologics are typically delivered intravenously or subcutaneously.²⁷² “[T]he markup of an infused medicine is greater in an inpatient setting than in a physician office, providing an incentive for institutions able to administer drugs in a setting that qualifies as inpatient.”²⁷³

Of course, there are misgivings from the private sector, as demonstrated by the current biosimilar litigation landscape, but existing patent-exclusivity periods exist to remedy those concerns. Admittedly, the outcome of patent litigation over manufacturing techniques could greatly affect biosimilar survival to market.²⁷⁴ Nevertheless, much-needed, long-established therapies should not be held hostage to a bureaucratically drawn-out approval process.

272. Phil Taylor, *Oral Biologics Delivery Still Elusive*, PMLIVE (Feb. 17, 2016), http://www.pmlive.com/pharma_intelligence/oral_biologics_delivery_still_elusive_908436.

273. Ralph Boccia et al., *supra* note 200.

274. For a summary of ongoing biosimilar litigation, see Michael Cottler, Joshua Whithill, & Alison Siedor, *The 2018 Biosimilar Litigation Landscape: A Primer*, BIOPHARMADIVE (Dec. 14, 2017), <https://www.biopharmadive.com/news/the-2018-biosimilar-litigation-landscape-a-primer/512982/>.