

BIOSIMILARS: COUNTERING SHORTAGES OF BIOTHERAPIES IN A GLOBAL AND LOCAL CONTEXT

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CONTENTS

I.	Introduction.....	360
II.	Biologics in a Global Context.....	362
III.	The Status of Biosimilar Law in Major Markets: 364	
A.	United States.....	364
B.	Europe.....	367
C.	China.....	368
D.	India.....	370
IV.	Current Global Initiatives to Address Drug Shortages and Access.....	371
A.	Agreement on Trade Related Aspects of Intellectual Property Rights.....	371
B.	Doha Declaration of the TRIPS Agreement.....	373
V.	Need for a Global Solution.....	375
VI.	Proposed Courses of Action.....	377
A.	Greater administrative and regulatory expertise is needed to address biologic shortages.....	379
B.	Biologics should be made in smaller quantities for niche markets.....	381
C.	International Patent Law Should be Reformed to Provide Specific Incentives for Developing Countries.....	382
VII.	Conclusion.....	383

I. INTRODUCTION

Drug shortages have been increasing in the United States, and have tripled between 2006 and 2011.¹ In less developed countries, drugs shortages are even greater.² Shortages of drugs and other therapies cause people to be denied access to medicines that are either already developed, or could be developed with existing technology.³

Between sixty-eight and seventy-seven percent of shortages are for biologic drugs,⁴ even though biologics only account for around thirty percent of all pharmaceuticals.⁵ Biologics are a class of drugs that are either produced by or composed of living material or once-living material, making

¹ C. Lee Ventola, *The Drug Shortage Crisis in the United States*, 36 PHARMACY & THERAPEUTICS 740, 749 (2011).

² C. JAMES ATTRIDGE & ALEXANDER S. PREKER, IMPROVING ACCESS TO MEDICINES IN DEVELOPING COUNTRIES APPLICATION OF NEW INSTITUTIONAL ECONOMICS TO THE ANALYSIS OF MANUFACTURING AND DISTRIBUTION ISSUES 22 (March 2005), <http://apps.who.int/medicinedocs/documents/s16743e/s16743e.pdf> [<https://perma.cc/K596-RLUQ>].

³ See generally *CDER Conversation: FDA's drug shortages prevention strategies*, U.S. FOOD & DRUG ADMIN. (Feb. 5, 2015), <http://www.fda.gov/Drugs/NewsEvents/ucm432474.htm> [<https://perma.cc/FLV9-HG2Z>].

⁴ John Horton, *Drug Shortages and You: Who's At Risk, What's the Fix?*, HUFFINGTON POST (Mar. 9, 2012 3:38 EST), http://www.huffingtonpost.com/john-horton/fda-drug-shortage_b_1311674.html [<https://perma.cc/G5QV-KS45>].

⁵ *Global Market Study Biological Drugs: North America to Remain as the Largest Biological Drug Market during the Forecast Period (2014–2020)*, PERSISTENCE MARKET RESEARCH (May 2015), <http://www.persistencemarketresearch.com/market-research/global-biological-drugs-market.asp> [<https://perma.cc/42ZN-BWCL>].

them difficult to manufacture.⁶ Unlike traditional, small molecule, chemical drugs such as Tylenol, Prozac, and Advil, biologics contain complex protein and sugar structures derived from natural sources such as plants, animals, and microorganisms.⁷ Biologics are vaccines, blood components, allergenics, gene therapy, and recombinant therapeutic proteins.⁸ They are currently used to treat life-threatening diseases such as cancer, tuberculosis, and HIV/AIDS.⁹

Due to their complexity and dependency on genetic and environmental factors, biologics are impossible to replicate identically.¹⁰ Therefore, truly “generic” versions of biologics cannot be made, and scientists refer to copy biologics as “biosimilars.” Because of this difficulty in replication, biologics and biosimilars already face serious shortages worldwide. Ensuring biosimilars are similar enough to the reference product is extremely important because small differences can cause severely different responses in patients. While no report has been made of a biosimilar that led to serious health consequences, just one incident of injury could halt approvals.¹¹

⁶ *How do Drugs and Biologics Differ?*, BIOTECHNOLOGY INNOVATION ORGANIZATION, <https://www.bio.org/articles/how-do-drugs-and-biologics-differ> [<https://perma.cc/55D6-7DBC>].

⁷ See Vinita Banthia, *Biosimilar Regulation: Bringing the United States Up to Speed With Other Nations*, 16 MINN. J.L. SCI. & TECH. 879, 882 (2015).

⁸ *What Are "Biologics" Questions and Answers*, FOOD & DRUG ADMIN., (Aug. 5, 2015), <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm> [<https://perma.cc/VZ6A-ZLNW>].

⁹ *Id.*

¹⁰ *Global Market Study*, *supra* note 5.

¹¹ The author searched different international databases and interviewed experts in the field to learn about any potential incidents of injuries or

This paper analyzes the global biologic and biosimilar market to develop possible solutions to shortages of biologics. First, this paper discusses the nature of the biologic market and explains the acceptance of follow-on biologics around the world, focusing on the United States, Europe, China, and India. Next, this paper addresses what the shortages mean for different countries. In the next section, this paper addresses steps that have already been taken to address these shortages worldwide. Finally, the paper addresses reasons for shortages of biologics in different parts of the world and proposes actions that will increase access of biologics in other countries and at home.

II. BIOLOGICS IN A GLOBAL CONTEXT

The global biologic market was worth around US \$161,057 million in 2014, and is anticipated to grow to US \$287,140 million by 2020, reflecting a compounded annual growth rate of 10.1% between now and then.¹² Key driving factors of this growth include the rise of chronic illnesses, the aging population, and government associations and organizations that are promoting the use of biologics for certain diseases.¹³

North America, particularly the United States, currently dominates the biologics market, especially with respect to innovative biologics. Europe and Asia follow, and both markets have a higher number of follow-on biologics

adverse effects from biosimilars on the market but was unable to find a single example.

¹² *Increasing Demand for Biological Drugs Market in America Boosting R&D Efforts*, EUROPLAT (Dec. 1, 2014), <http://www.europlat.org/increasing-demand-for-biological-drugs-market-in-america-boosting-rd-efforts.htm> [<https://perma.cc/25GK-NDUT>].

¹³ *Global Market Study*, *supra* note 5.

than the United States.¹⁴ Markets in Europe, Asia, and Latin America have been able to embrace follow-on biologics faster than the United States due to less stringent regulatory and intellectual property restrictions.¹⁵ Currently, biosimilars and other non-original biologics make up 10% of emerging countries' biologics market, compared to only 0.5% for developed countries.¹⁶

Many of these middle-income, emerging countries have accepted biosimilars without creating a separate regulatory pathway. Instead, these countries use the same approval pathway as has been used for generic, small molecule chemical drugs.¹⁷ Recently, some emerging countries are developing new regulatory standards for biosimilars that recognize the specific risks associated with large molecule drugs.¹⁸ These countries face the questions of whether copy biologics that have already been approved under the generic pathway will remain on the market, or need to be re-approved under the new system.¹⁹

Because biosimilars require precisely controlled environmental, genetic, and procedural factors for manufacturing, the approval pathway for biosimilars in most countries is also more stringent than the approval pathway for generic drugs. Therefore, the cost of producing and marketing a biosimilar (compared to a biologic) does not

¹⁴ Feng Zengkun, *The brave new world of biosimilars*, Future Ready Singapore (Jan. 23, 2017), <https://www.futurereadysingapore.com/2017/the-brave-new-world-of-biosimilars.html> [<https://perma.cc/EH3S-7Q7M>].

¹⁵ *Id.*

¹⁶ *Id.*

¹⁷ See RODEINA CHALLAND, *BIOSIMILARS IN EMERGING MARKETS: IS IT A LEVEL PLAYING FIELD?* (Dec. 2015).

¹⁸ *Id.*

¹⁹ *Id.*

produce the same cost savings for a manufacturer as a generic drug would. The fact that biosimilars cannot gain patent protection means it is challenging for the manufacturer to recover the costs of production. The following section discusses the current status of biosimilar law in the United States, Europe, China, and India.²⁰

III. THE STATUS OF BIOSIMILAR LAW IN MAJOR MARKETS:

A. *United States*

On March 6, 2015, the U.S. Food and Drug Administration (FDA) approved the United States' first biosimilar—Zarxio, a cancer therapy drug.²¹ Zarxio was developed by Sandoz, Inc., as a copycat version of Amgen Inc.'s Neupogen, originally approved in 1991.²² Amgen immediately filed suit against Zarxio's approval and obtained an injunction in the Federal Circuit, preventing Sandoz from "marketing, selling, offering for sale, or importing into the United States its FDA-approved ZARXIO® biosimilar product."²³ Sandoz filed an opposition to the injunction with the Federal Circuit, but the

²⁰ Erwin A. Blackstone & P. Fuhr Joseph, *The Economics of Biosimilars*, 6 AM. HEALTH & DRUG BENEFITS 469, 470 (2013).

²¹ FDA Approves First Biosimilar Product Zarxio, FDA NEWS RELEASE (last visited Nov. 26, 2015), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm> [<https://perma.cc/MV72-JWQX>].

²² *Id.*

²³ Margaux L. Nair, et al., *Amgen Prevails on Temporarily Excluding Zarxio® From Market*, K&L GATES (May 8, 2015), <http://www.klgates.com/amgen-prevails-on-temporarily-excluding-zarxio-from-market-05-08-2015/> [<https://perma.cc/YL8S-CPXS>].

opposition was denied.²⁴ However, on September 3, 2015, the Federal Circuit denied Amgen's motion to renew the injunction, without an explanation, and Zarxio was subsequently the first biosimilar to enter U.S. market.²⁵

In 2010, five years before Zarxio's approval, the U.S. Congress had passed the Biologics Price Competition and Innovation Act (Biosimilars Act), outlining an abbreviated approval pathway for biosimilars.²⁶ Because the biosimilar approval pathway is not as abbreviated as it is for generic drugs, the shortage for biologics has led to an especially severe shortage of biologic drugs, such as oncological vaccines.²⁷

The biosimilar approval pathway requires the applicant to demonstrate that the biosimilar is similar or "bioequivalent" to the reference product through analytical studies, animal studies, and at least one clinical study.²⁸ These tests must collaboratively demonstrate that the biosimilar and reference product both "utilize the same mechanism . . . for the condition or conditions of use prescribed," where the biologic has been previously

²⁴ *Id.* See also *BREAKING NEWS—Sandoz launches biosimilar product Zarxio in the U.S.*, GOODWINPROCTOR LLP: BIG MOLECULE WATCH BLOG (Sep. 3, 2015), <http://www.bigmoleculewatch.com/2015/09/03/breaking-news-sandoz-launches-biosimilar-product-zarxio-in-the-u-s/> [<https://perma.cc/K8VR-GSU8>].

²⁵ Lisa Mueller & Wei Yan, *Update in Amgen v. Sandoz*, BRIC WALL, (Sep. 3, 2015) <https://bricwallblog.com/2015/09/03/update-in-amgen-v-sandoz/> [<https://perma.cc/AKC2-KMVV>].

²⁶ Ryan Timmis, *The Biologics Price Competition and Innovation Act: Potential Problems in the Biologic-Drug Regulatory Scheme*, 13 NORTHWESTERN J. TECH. & INTELL. PROP. 215, 221 (2015).

²⁷ Hagop Kantarjian, *Chemotherapy Drug Shortages in the United States Revisited*, 10 J. ONCOLOGY PRACTICE 329, 330 (2014).

²⁸ 42 U.S.C. § 262(k)(2) (2012).

approved for that condition.²⁹ “The route of administration, the dosage form, and the strength of the biological product [must be] the same as those of the reference product.”³⁰ Finally, “the facility in which the biological product is manufactured, processed, packed, or held [must meet] standards designed to assure that the biological product continues to be safe, pure, and potent.”³¹

Once the biosimilar application is submitted to the FDA, the applicants must give the reference biologic a copy of its biosimilar application within 20 days of receiving confirmation that the FDA has accepted the application.³² The reference biologic has a chance to respond to the biosimilar applicant with a list of all the patents it believes the biosimilar will be infringing.³³ The biosimilar applicant may then respond to the reference product owner with a statement that the asserted patents are either invalid, will not be infringed by the biosimilar, or that the biosimilar will be commercially marketed before the expiration of the patent(s).³⁴ Eventually, the reference biologic owner and the biosimilar applicant are expected to engage in good faith negotiations to decide which patents can be reasonably included in infringement claims.³⁵ In the event that the parties fail to agree on a list, the reference product owner has 30 days to file for a permanent injunction against the

²⁹ *Id.*

³⁰ *Id.*

³¹ *Id.*

³² *Id.* § 262(1)(2).

³³ *Id.* § 262(1)(3)(A).

³⁴ *Id.* § 262(1)(3)(B).

³⁵ Janice A. Vatland, *Top Actions to Consider in Light of the Biosimilar Act* 29 WESTLAW J. PHARMACEUTICAL 1, 3 (2013).

biosimilar applicant's marketing of the biosimilar.³⁶ If the reference biologic fails to meet this deadline, remedies for any of infringement are limited to reasonable royalties.³⁷

The Biosimilars Act grants twelve years of exclusivity to all original biologics, which apply in addition to any patent rights. No biosimilar can be approved during this time.³⁸ The Biosimilars Act further provides that no biosimilar applicant can even submit an application for approval in the first four years after a reference product is approved.³⁹

B. Europe

While the European Union has been a lead innovator of biologics, it has also embraced biosimilars faster than the United States. In 2003, the European Medicines Agency (EMA) was given authority to oversee regulation of biosimilars all around Europe, in an effort to centralize the approval effort.⁴⁰ The EMA released guidance on the approval process in 2005 and the first biosimilar was approved in 2006.⁴¹ To date, twenty-two biosimilars have been approved in Europe; however, two approvals have been

³⁶ *Id.*

³⁷ *Id.* at 4.

³⁸ 42 U.S.C. § 262(k)(7)(A).

³⁹ *Id.* § 262(k)(7)(B).

⁴⁰ See Francis Megerlin et al., *Biosimilars and the European Experience: Implications for the United States*, 32 HEALTH AFF., 1803, 1804-05 (2013). For an updated list of all approved biosimilars see EUROPEAN MEDICINES AGENCY, <http://www.ema.europa.eu/ema> [<https://perma.cc/4T6C-FLDF>] (follow “find medicine”; then follow “Human Medicines”; then follow “browse by type” tab; then follow “biosimilars”) (last visited Apr. 4, 2016).

⁴¹ Jacob F. Siegel & Aron Fischer, *Ten Years of Biosimilars in Europe*, BIOLOGICSBLOG (Dec. 8, 2015), <http://www.biologicsblog.com/blog/ten-years-of-biosimilars-in-europe/> [<https://perma.cc/EF7K-5PV5>].

cancelled, leaving twenty biosimilars on the current market.⁴² The two biosimilar application cancellations were voluntarily submitted by the manufacturers, for unknown reasons.⁴³ There have been no recorded incidents of large-scale adverse effects of biosimilars in Europe.

Biosimilars in Europe have consisted of monoclonal antibodies, epoetins, growth hormones, insulins, and filgrastims.⁴⁴ They have been 20–30% cheaper than their reference biologics and are expected to cut E.U. health costs by \$11 to \$33 billion by 2020.⁴⁵ Savings from biosimilars in Europe are expected to rise significantly as more biosimilars enter both the E.U. and U.S. markets because this will incentive manufacturers have to develop more biosimilars.⁴⁶ Some challenges with the E.U. biosimilar market includes maintaining sufficient regulation, and naming criteria for the follow-on biologics.⁴⁷

C. *China*

China has one innovative biologic drug that has been developed locally.⁴⁸ Apart from this one biologic, China's

⁴² Bantia, *supra* note 7, at 890.

⁴³ *Id.*

⁴⁴ Mari Serebrov, *BioWorld Biosimilar: A Global Perspective of a New Market: Opportunities, Threats and Critical Strategies*, BIOSIMILARS: A GLOBAL PERSP. OF A NEW MKT., OPPORTUNITIES, THREATS, AND CRITICAL STRATEGIES 22 (2014), http://images.info.science.thomsonreuters.biz/Web/ThomsonReutersScience/%7B15f315b6-f2cd-4368-93ce-ccf7cd46c649%7D_Biosimilars2014_-_sample3.pdf [<https://perma.cc/VWH8-VE3F>].

⁴⁵ *Id.*

⁴⁶ *Id.*

⁴⁷ *Id.*

⁴⁸ Andy Tsun, et al., *The Chinese Biologics Drug Market: Demand and Execution*, DRUG DISCOVERY WORLD (Spring 2015), <http://www.ddw->

biologic market is dominated by follow-on or non-original biologics, which make up 96% of the Chinese biologics market.⁴⁹ For example, China has approved 21 monoclonal antibodies that have been developed overseas but are now manufactured in China or imported from other countries.⁵⁰ Nearly all biologics available in China are either imported and sold for high premiums, or manufactured by local biosimilar manufacturing companies and approved under the same pathway as small molecule generic drugs.⁵¹

The China Food and Drug Administration (CFDA) published its first draft guidance in October 2014 for approval of biosimilars.⁵² The guidance establishes the basic research, development, and assessment needed for a biosimilar to be deemed comparable to the reference product.⁵³ The guidance recommends procedures to establish that “no or little difference” is found during “comparability testing”; in which case subsequent comparability tests may be eliminated.⁵⁴ The draft guidance is not legally binding and more regulation and guidance is expected soon to clarify biosimilar approval procedures.⁵⁵

online.com/business/p303320-the-chinese-biologics-drug-market:-demand-and-execution-spring-15.html [https://perma.cc/6C5P-NZ9K].

⁴⁹ *Id.*

⁵⁰ *Id.*

⁵¹ *Id.*

⁵² *China Announces Final Biosimilar Guideline*, ROPES & GRAY (Mar. 6, 2015), <https://www.ropesgray.com/newsroom/alerts/2015/March/China-Announces-Final-Biosimilars-Guideline.aspx> [https://perma.cc/43JW-5A4Q].

⁵³ *Id.*

⁵⁴ *Id.*

⁵⁵ *Id.*

D. *India*

The Indian Department of Biotechnology (DBT) and Central Drugs Standard Control (CDSCO) issued a biosimilar guideline in June 2012, and an updated version in March 2016, where both documents are similar to biosimilar regulation in the United States and Europe. India already has eight biosimilars on the market that were approved under the 2012 guidance, and up to 60 that were approved prior to the guidance.⁵⁶ Under the guidance, a biosimilar must pass a “quality characterization,” a detailed requirement for animal studies, and clinical studies.⁵⁷ Clinical requirements may be reduced under “demonstration of comparability of product (similarity to authorized reference biologic) and the consistency in production process, which may vary depending on the characteristics of the already authorized reference biologic.”⁵⁸ The reference product must either be licensed in India, or must have been in use for at least 4 years in a highly regulated and monitored market.⁵⁹ The guidance also states that the biosimilar applicant must generate some clinical data locally.⁶⁰

Like China, India has also been approving biosimilars under the same regulatory pathway as generics, which will likely create two tiers of biosimilars—those

⁵⁶ Zachary Brennan, *India Releases New Biosimilar Guidance*, REG. AFF. PROFESSIONALS SOC’Y (Mar. 28, 2016), <http://www.raps.org/Regulatory-Focus/News/2016/03/28/24638/India-Releases-New-Biosimilars-Guidance/> [https://perma.cc/Z443-9RLW].

⁵⁷ *Guidelines on Biosimilar Biologics: Regulatory Requirements for Marketing Authorization in India*, GOV’T OF INDIA 1,4 (2012), <http://dbtbiosafety.nic.in/Files%5CCDSCO-DBTSimilarBiologicsfinal.pdf> [https://perma.cc/Q299-U54Y].

⁵⁸ *Id.*

⁵⁹ *Id.*

⁶⁰ *Id.*

approved before the new guidance and those approved after. It is yet to be seen how India and China will distinguish between these two classes of biologics.⁶¹

IV. CURRENT GLOBAL INITIATIVES TO ADDRESS DRUG SHORTAGES AND ACCESS

Today, it is important to find ways to increase access to pharmaceuticals globally, with a solution that addresses the unique needs of each country. Factors such as increased international travel, more international trade, specifically of agricultural products, and growing bacterial resistance prompt faster spread of disease worldwide. For example, the Zika and Ebola virus outbreaks of the last two years have been spread across the world within months due to international travel. These changes in the spread of disease means no country is isolated from global epidemics, and all nations must work toward a unified response. The following section describes the current status of international treaties and agreements that aim to address economic development of different countries and access to essential medicines.

A. Agreement on Trade Related Aspects of Intellectual Property Rights

By the 1980s, members of the World Trade Organization (WTO) recognized the need for an international intellectual property (IP) agreement to address the growth of international innovation and trade.⁶² Hence,

⁶¹ CHALLAND, *supra* note 17.

⁶² *Intellectual property: protection and enforcement*, WORLD TRADE ORGANIZATION (last visited Nov. 21, 2015), https://www.wto.org/english/thewto_e/whatis_e/tif_e/agrm7_e.htm [<https://perma.cc/5SDG-EJYL>]. See Samuel Kortum & Josh Lerner, *What Is Behind the Recent Surge in Patenting?*, 28 RES. POL'Y 1, 21 (1999).

between 1986 and 1994, WTO member nations drafted the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement).⁶³

The TRIPS Agreement set out minimum rights and protections that an owner of a creative work would enjoy in all member countries. First, the most-favored-nation (MFN) provision ensures that member nations cannot play favorites with certain countries. MFN states that if a member nation grants one of its trading partners a special IP protection, it must grant that protection to all other member nations.⁶⁴ Second, the national treatment (NT) provision states that each member nation must provide the same IP protection to foreign-produced goods as it does to locally or nationally-produced goods.⁶⁵ The Agreement addresses copyrights, trademarks, geographical indications, patents, industrial designs, and trade secrets.⁶⁶ Nations are not required to provide this equal treatment before the product enters the nation—hence, countries are able to levy taxes on importation before a good enters the country.⁶⁷

The TRIPS Agreement provides specific provisions relating to patents. First, it requires that patents be available in every field, including for life-saving pharmaceuticals and medical devices, which were previously not patentable in

⁶³ Kevin C. Kennedy, *The GATT-WTO System At Fifty*, 16 WIS. INT'L L.J. 421, 442–44 (1998).

⁶⁴ *Principles of the Trading System*, WORLD TRADE ORGANIZATION, (last visited Nov. 21, 2015), https://www.wto.org/english/thewto_e/whatis_e/tif_e/fact2_e.htm#national [<https://perma.cc/6A4M-2MXS>].

⁶⁵ Agreement on Trade-Related Aspects of Intellectual Property Rights arts. 3–4, Apr. 15, 1994, 33 I.L.M. 81 [hereinafter TRIPS Agreement].

⁶⁶ *Overview: the TRIPS Agreement*, WORLD TRADE ORGANIZATION (last visited Nov. 21, 2015), https://www.wto.org/english/tratop_e/trips_e/intel2_e.htm [<https://perma.cc/385V-KWLU>].

⁶⁷ *Principles of the Trading System*, *supra* note 64.

many countries.⁶⁸ Exceptions may be made for countries that need to exclude patents on diagnostic, therapeutic and surgical methods,⁶⁹ but only to protect “*ordre public* or morality,”⁷⁰ which has not been clearly defined and continues to be debated.⁷¹ Exceptions may also be made in cases of “national emergency or other circumstances of extreme urgency,” where a government may circumvent patent rights without authorization of the right holder.⁷² This allows governments to occasionally grant compulsory licenses for pharmaceutical products; but again, there is considerable debate regarding what constitutes a national emergency, and when this exception is permissible. Finally, the TRIPS Agreement sets a uniform patent term of 20 years for all nations.⁷³

B. *Doha Declaration of the TRIPS Agreement*

Many developing nations felt that the TRIPS Agreement sought to impose U.S. patent laws on the rest of the world, without appreciating each countries’ unique needs and development stage. In response to the controversies, member nations reconvened to define some of the uncertain concepts. Developing countries wanted the right to grant compulsory licenses during national health emergencies, at each country’s own discretion.⁷⁴ The United States argued

⁶⁸ TRIPS Agreement, *supra* note 65 art. 27.

⁶⁹ *Id.*

⁷⁰ *Id.*

⁷¹ *Id.*

⁷² *Id.* art. 31.

⁷³ *Id.* art. 33.

⁷⁴ Developing countries often do not yet have the infrastructure to implement the patent systems already in place in the United States. For example, developing countries do not have patent law in their law school curriculum due to lack of qualified teachers; and they do not

for strict implementation of patent rights by all nations.⁷⁵ This debate led to the creation of the 2001 Doha Declaration TRIPS and Public Health (Doha Declaration).⁷⁶

The Doha Declaration provides different strategies to enable developing and least developed nations gain access to pharmaceuticals during times of national emergencies, and clarifies some of the ambiguous terms of the TRIPS Agreement.⁷⁷ It confirmed the importance of the “right to protect public health and, in particular, to promote access to medicines for all, and affirmed “the right of WTO Members to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility for this purpose.”⁷⁸

have IP offices or courts due to lack of judges and enforcers. See Kimberly A. Czub, *Argentina’s Emerging Standard of Intellectual Property Protection: A Case Study of the Underlying Conflicts Between Developing Countries, TRIPS Standards, and the United States*, 33 CASE W. RES. J. INT’L L. 191, 220 (2001).

⁷⁵ See generally Robert C. Bird, *Developing Nations and the Compulsory License: Maximizing Access to Essential Medicines While Minimizing Investment Side-Effects*, 37 J.L. MED. & ETHICS 209, 210 (2009).

⁷⁶ James Thuo Gathii, *The Legal Status of the Doha Declaration on TRIPS and Public Health Under the Vienna Convention on the Law of Treaties*, 15 HARV. J.L. & TECH. 291, 292 (2009).

⁷⁷ James Love, *What the 2001 Doha Declaration Changed*, KNOWLEDGE ECOLOGY INTERNATIONAL (Sep. 16, 2011 5:10 CDT), <http://keionline.org/node/1267> [<https://perma.cc/8GAN-TXL9>]; Haochen Sun, *The Road to Doha and Beyond: Some Reflections on the TRIPS Agreement and Public Health*, 15 EUR. J. INT’L L. 123, 148 (2004)(discussing the pressures from different academics and governments after the enactment of TRIPS Agreement that led to the Doha Declaration), <http://www.ejil.org/pdfs/15/1/335.pdf> [<https://perma.cc/DHL5-VAZU>].

⁷⁸ World Trade Organization, Ministerial Declaration on the TRIPS Agreement and Public Health of 14 November 2001, WTO Doc. WT/MIN(01)/Dec/2 (2001), ¶ 4, https://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.pdf [<https://perma.cc/GS5H-XLGH>].

In addition, the Doha Declaration clarified that each country has the right to define a national emergency for itself, and that epidemics of all diseases can always qualify as national emergencies. The Doha Declaration further clarified that compulsory licenses are permissible at any time during these national emergencies, even after a developing nation has fully adopted the TRIPS Agreement.⁷⁹

Finally, recognizing that compulsory licenses may not be feasible for least developed nations that lack resources to manufacture the drugs within their borders, the Doha Declaration provided the option of parallel importation.⁸⁰ Parallel importation allows nations to negotiate with a government or patented pharmaceutical company in another country to send certain amounts of pharmaceuticals to the developing nation in return for reasonable compensation.⁸¹ Usually, the pharmaceutical companies will be able to sell the drugs for cheaper in poorer countries, and recover costs with higher prices in developed countries.⁸² Alternatively, third-party countries could apply for compulsory licenses, produce the biologic drugs, and provide them to least developed countries through parallel importation.⁸³

V. NEED FOR A GLOBAL SOLUTION

One criticism of the TRIPS Agreement has been that its strict patent regulations incentivize branded drugs more

⁷⁹ Love, *supra* note 77. *Parallel Imports*, WORLD HEALTH ORGANIZATION, (last visited Nov. 29, 2015), [http://web.archive.org/web/20151126203743/http://www.who.int/trade/glossary/story070/en/\[https://perma.cc/9537-4BB2\]](http://web.archive.org/web/20151126203743/http://www.who.int/trade/glossary/story070/en/[https://perma.cc/9537-4BB2]).

⁸⁰ *Id.*

⁸¹ *Id.*

⁸² *Id.*

⁸³ ATTRIDGE & PREKER, *supra* note 2, at 28.

than generic drugs. Worldwide, shortages are greater for generic drugs than patented drugs, once a drug's patent term has run its course.⁸⁴ This means that often, while the branded version of a drug will still be available, the generic version will be unavailable or discontinued, leaving only the expensive version on the market. This imbalance restricts access to pharmaceuticals in the developing world, while providing monopolies and excessively high rewards for branded drug companies which are primarily located in developed countries.⁸⁵

While parallel importation and compulsory licenses are technically permissible under the TRIPS Agreement, countries such as the United States have imposed trade sanctions and other pressures to dissuade countries from implementing them, even in the face of national crises. For example, when Argentina and Brazil both decided to keep compulsory licenses as a viable option under their patent laws, the U.S. put both countries on its Special 301 Priority Watch List and imposed trade sanctions against both countries.⁸⁶

The U.S. argues that strict adherence to the TRIPS Agreement will benefit developing countries in the long run by encouraging foreign investment and foreign trade. Although this may be true for some middle income countries, many of these countries are facing health emergencies that are a more immediate priority over

⁸⁴ John H. Barton, *TRIPS And The Global Pharmaceutical Market* 23 HEALTH AFF. 146, 150 (May 2004), <http://content.healthaffairs.org/content/23/3/146.full#sec-6> [<https://perma.cc/5PK3-YXSG>].

⁸⁵ *Id.*

⁸⁶ See Czub, *supra* note 74, at 228 (discussing the trade sanctions and WTO dispute proceedings the United States brought against Argentina for refusing to enact patent laws under the U.S. interpretation of the TRIPS Agreement).

encouraging foreign trade.⁸⁷ In addition, some developing and least developed countries do not have the foundation to implement the TRIPS Agreement as they lack resources to encourage development of new treatment, and are unable to benefit from patent rights. In particular, adopting strict IP laws for pharmaceuticals or other life-saving medical technologies has consequences that can set nations behind in their economic development.⁸⁸

Due to the changing nature of biologic and biosimilar law, and the globalization of diseases, it is imperative that the world unite to find a system that improves access to biologics around the world. The following section proposes a multi-dimensional system aimed at reforming patent rights and administrative procedures, as well as biologics manufacturing and testing techniques.

VI. PROPOSED COURSES OF ACTION

The reasons for biologic shortages are different between nations, and it is important to consider all causes of the shortages to develop a comprehensive solution. For example, biologic shortages in developing countries are often caused by lower manufacturing capacities, high demand for certain treatments, and economic and social restrictions imposed by developed nations.⁸⁹ Developing countries also tend to have larger numbers of counterfeit and

⁸⁷ Edson Beas Rodrigues Junior & Bryan Murphy, *Brazil's Prior Consent Law: A Dialogue between Brazil and the U.S. Over Where the TRIPS Agreement Currently Sets the Balance Between the Protection of Pharmaceutical Patents and Access to Medicines* 16 Alb. L.J. Sci. & Tech. 423, 434 (2006) (demonstrating that Brazil's economy was improved after taking stricter measures to implement TRIPS).

⁸⁸ ATTRIDGE & PREKER, *supra* note 2, at 32.

⁸⁹ Bea Perks, *Conference Report: Drug Shortages and Ensuring the Quality of Medicine*, EUR. SOC'Y ONCOLOGY PHARMACY 38, 40 (2013).

sub-quality drugs on the market.⁹⁰ It is estimated that 37 percent of the drugs on the market in developing countries are of poor quality or completely ineffective.⁹¹ Furthermore, poorer people are more susceptible to online scams and black market schemes because they are more desperate to find cheap treatment. These factors contribute to the low supply of approved, high-quality biosimilars.⁹²

In contrast, shortages in the United States and other developed economies are most often caused by safety concerns in manufacturing facilities, imbalances in the supply/demand ratio, burdensome regulation, intellectual property laws, a lack of raw materials, and business decisions to discontinue some drug productions. Hence, drug shortages in these countries may be caused by complex issues that arise at different stages of the manufacturing process.⁹³

Middle-income countries such as India, China and Brazil manufacture significant numbers of generic biologics, and also have a higher need for these products. Some reasons why these markets will be able to produce biosimilars on a shorter time frame than other countries is the low cost of clinical trials, the less-burdensome procedures for finding participants for clinical studies, reduced patent restrictions, cheaper labor and equipment, reduced regulation, and more leeway afforded to physicians

⁹⁰ *Id.*

⁹¹ *Id.*

⁹² *Counterfeit Drugs*, Centers for Disease Control and Prevention, (last visited Nov. 29, 2015), <http://www.cdc.gov/features/counterfeitdrugs/> [<https://perma.cc/YR9F-WRZS>].

⁹³ *CBER-Regulated Products: Possible Causes of Shortages*, FOOD & DRUG ADMIN, (last updates Aug. 9, 2013), <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/Shortages/ucm351909.htm> [<https://perma.cc/WJ4A-7APS>]. See also Ventola, *supra* note 1, at 749.

to use therapies for different conditions.⁹⁴ However, these countries still lag behind in their development of branded pharmaceuticals.⁹⁵ In addition, many overseas-manufactured biologics are not approved in the United States due to excessive regulatory burdens.⁹⁶

Although more guidance and progress in the Indian and Chinese biosimilar industries is expected, some challenges with the countries' systems are still hindering progress. Currently, India and China each hold about 8% share of the global biologics market, while the U.S. and Europe hold 35.9% and 26.1% of the global biologics market, respectively.⁹⁷ Furthermore, the U.S. and Europe have greater numbers of innovative products, while India's and China's markets are composed primarily of biosimilars.⁹⁸ The next few sections discuss three ways to address these discrepancies and shortcomings of the global biologics market. These solutions include greater administrative and regulatory expertise, patent law reform, and targeted therapies.

A. Greater administrative and regulatory expertise is needed to address biologic shortages.

First, countries such as India and China face a shortage of qualified regulatory staff to evaluate and monitor

⁹⁴ Eric Palmer, *China, India Lose Some Appeal for Biologics Manufacturing*, FIERCEPHARMA (July 10, 2013), <http://www.fiercepharmamanufacturing.com/partnering/china-india-lose-some-appeal-for-biologics-manufacturing> [<https://perma.cc/WKL4-QLEL>].

⁹⁵ *Id.*

⁹⁶ *Id.*

⁹⁷ *Id.*

⁹⁸ *Id.*

the biosimilars in the marketplace. The product approval backlog is daunting for any company considering market entry. For example, it takes nearly 18 months for approval of a clinical trial in China, compared to 30 days in the US. The fact that both India and China want a certain number of clinical trials performed within their borders adds further costs and bureaucracy.⁹⁹

To address these issues, middle-income countries should focus on training personnel on the regulation of biologics, and developing standardized procedures for the approval of biologics and biosimilars. The new guidelines have already increased the numbers of safe biosimilars on the market, and more clear guidelines will continue this trend.¹⁰⁰ Once the biosimilar market is more robust, more workers will be enticed to go into the field of regulation.

In addition, the different biosimilar markets around the world should streamline their efforts to reduce the overall numbers of trials necessary. While some geographic clinical data may be obtained for drugs that could vary between populations, these tests should only occur at later stages of the testing process. Information and data should be shared regularly and openly between nations and companies, for pharmaceuticals. To incentivize companies in the U.S. to share data, middle income countries may offer clinical trial test patients, raw material, and other resources that are beneficial to the U.S. company. Countries may also agree to harmonize tests and mutually share data. These mutually beneficial agreements between developing and developed countries' manufacturers will lead to better longer term

⁹⁹ This shortage of expertise is seen globally, including in the United States and Europe, but is especially problematic in some countries.

¹⁰⁰ *Biologics & Vaccines*, THREE RS MICROSITE, <http://3rs.ccac.ca/en/testing-and-production/tp-testing/biologics-and-vaccines.html> [<https://perma.cc/Y5Q5-3EQW>] (last visited Jan. 28, 2017).

solutions as opposed to simply exchanging money for trial patients.¹⁰¹

B. Biologics should be made in smaller quantities for niche markets.

Many developing countries import drugs from developed countries and end up paying high premiums. Hence, global efforts should encourage more local manufacturing in China, India, and other middle-income countries.¹⁰² Setting-up smaller markets that produce niche, population-specific products will reduce “blockbuster” drugs and decrease the demands for individual products.¹⁰³ Currently, biologics may not be narrowly tailored to the unique needs of individual populations. Better diagnostics and increased post-market surveillance will enable companies to tailor each drug to specific demographics and reduce waste. While this may lead to increased costs at the forefront, overall savings will be seen with time.¹⁰⁴ In addition, the use of different materials, environments, and subjects will advance the discovery of novel, geographic-specific therapies faster. Therefore, governments should invest in small, quality-controlled manufacturing sites locally, and implement robust post-market surveillance to expedite the biologics market.¹⁰⁵

¹⁰¹ CHALLAND, *supra* note 17, at 5.

¹⁰² Tsun, *supra* note 51.

¹⁰³ Howard L. Levine, *A World of Biomanufacturing: Shortages or Global Glut?*, BIOPROCESS INTERNATIONAL CONFERENCE 1, 20 (May 19, 2010), http://www.bptc.com/sites/default/files/presentations/levine_hl-a_world_of_biomanufacturing-shortages_or_global_glut.pdf [<https://perma.cc/HL2R-F9TK>].

¹⁰⁴ *Id.*

¹⁰⁵ *See id.* at 29.

C. *International Patent Law Should be Reformed to Provide Specific Incentives for Developing Countries.*

The current patent system fails to encourage development of generic and innovator drugs in developing countries. First, least developed countries largely lack research and manufacturing capacities, and will not benefit from patent rights in the near future. Second, emerging economies develop a large number of generic drugs which do not qualify for patent protection. Because exclusivity will increase shortages in the long run, governments should incentivize development in other ways, such as through a robust biologics customer base. Current shortages are exacerbated by the fact that manufacturers are not able to access a large part of the market because of the high cost. Therefore, if governments ensured that patients are reimbursed for locally-produced biosimilars, insurances cover biosimilar versions of biologics, and biosimilar drugs are treated equal or better in markets, they will be more successful. Governments could also promise developers better access to hospitals and doctors for clinical trials. These non-patent incentives will increase therapies while providing rewards for manufacturers.

The U.S. and E.U. can also reduce costs of biosimilars and biologics around the world by accepting biosimilars faster, which will lead to a growth in the development of new therapies and a drop in prices for existing ones. However, the nature of biologics and the skill level required to develop a biosimilar warrants some exclusivity for follow-on products.¹⁰⁶

¹⁰⁶ *Id.* at 31.

VII. CONCLUSION

This paper examines the current state of biologic drug shortages in a global context by addressing individual and local needs. This paper finally argues that three methods of incentivizing biosimilars in the U.S. and around the world are: changing the current administrative system to reduce barriers and delay in regulation, embracing smaller-scale manufacturing facilities, and reforming patent law around biologics.