



Biogenerics or Biosimilars?

Discussing the Present,
Considering the Future

By Rachel Chu and Dr Meir Pugatch

 STOCKHOLM NETWORK

Biogenerics or Biosimilars? –

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Foreword

The Stockholm Network's health and welfare programme examines healthcare policymaking from the perspective of the consumer, aiming to identify policies which can create a world in which the patient has greater information and choice.

The study of healthcare policy is particularly demanding because the pace of scientific change is now so rapid. Policymakers constantly struggle to make sure they are keeping up with the ever changing developments and that the current legislative and regulatory framework is in line with new thinking.

The development of biological drugs poses one such challenge – a completely new form of medicinal treatment arrives into the marketplace which upsets expectations, changes business models and requires a different mindset to its more straightforward predecessors.

How can patient safety be maximised while not causing undue delays in getting new medicines and treatments to the market? What balance should be struck between rewarding innovators and allowing competition? How do different jurisdictions handle this problem and is any kind of best practice starting to emerge?

Very few policy papers have yet been written by think tanks on the issue of biosimilars and even less about their impact on healthcare policymaking. This study attempts to explain the background and open the debate to a wider audience as well as to make a series of policy recommendations which we believe are in the best interest of both patients and innovators.

Helen Disney
CEO, Stockholm Network
October 2009

Executive Summary

The first generation of biological drugs, which have introduced many revolutionary treatments to life-threatening and rare illnesses, is currently facing patent expiration. As a result, research-based and generics pharmaceutical companies alike are pursuing the opportunity to develop “generic” substitutes to original biologics, which are also known as biosimilars.

Yet the field of biosimilars presents several important challenges – safety, regulatory, legal and economic – which are the topic of discussion across the globe. Most of these discussions stem from the idea that, unlike the relatively straightforward process of introducing a generic equivalent to an original drug based on a new chemical entity (NCE), the process of introducing a biosimilar to an original biological drug is far more complex.

With this in mind, the purpose of this paper is to examine the various challenges that biosimilars raise, particularly with regards to the regulatory framework, commercial opportunities, intellectual property rights (IPRs) and most importantly of all, to public safety.

The paper examines several discussions related to safety and regulatory issues, including the amount of clinical studies that should be required as part of the testing and approval process, as well as whether the biosimilar should be considered “automatically” interchangeable with the original biologic.

Discussions surrounding the commercial implications of biosimilars are also considered. In particular, given the complexity of biological drugs, which will only continue to grow with the next generation, the paper notes that the existing and future biosimilar players may include both some of the largest generics companies and some research-based companies. Overall, it is suggested that the biologics market may see fewer biosimilar competitors as well as a smaller gap in prices between biosimilars and original biologics.

Furthermore, the paper examines debates surrounding intellectual property (IP) issues, especially concerning patent protection and data exclusivity. Patent-related discussions include the potential for biosimilar companies to “design around” relevant patents of original biologics, with the result that patent protection may not be as robust for biological drugs as they are for NCE-based drugs, as well as the importance of streamlining the resolution of patent disputes, based on the idea that they will become more complicated with biosimilars. Debates related to data exclusivity, which has tended to be a hot topic especially in the US, mainly concern the appropriate length of data exclusivity, as well as whether to afford exclusivity to biosimilar companies, given that they will probably be required to submit their own clinical data.

In the midst of these and other discussions surrounding biosimilars, several countries and regions have created - or are in the process of creating - regulatory pathways that seek to address the various debates. This paper takes four

of the most relevant pathways, namely the EU, WHO, Canada and the US (where legislation is still under way), as case studies and evaluates in particular whether these pathways have resolved the safety and IP dilemmas discussed in the previous section.

With regard to safety issues, the paper finds that submitting the results from at least one or two clinical trials relating to the new biosimilar seems to be the standard among almost all of the cases. With regard to the issue of “interchangeability” (i.e. the possibility of providing the patient with a biosimilar substitute to the original biologic drug), most countries seem to ban this practice altogether (i.e. Germany, Sweden, Spain and the Netherlands). Alternatively, some countries, such as Canada, recommend rigorous scientific and clinical data before the decision is taken.

In summary, the paper presents the following policy considerations for future biosimilar frameworks:

- 1) Legislation should require a baseline scientific comparison of the biosimilar with the original drug.
- 2) Based on the differences identified in the scientific comparison with the original biologic, the legislation should identify the level of clinical data that will be needed to evaluate and approve the biosimilar.
- 3) Legislation should call for post-marketing safety studies in order to monitor any potential differences in safety and efficacy between the biosimilar and original drug that become apparent once a biosimilar enters the market.
- 4) Legislation should define the standard and criteria for interchangeability of the biosimilar with the original drug.
- 5) Finally, legislation should provide sufficient incentives to research-based companies via IP protection. It should ensure that patent protection is not eroded with the entry of biosimilars. If appropriate, the term of data exclusivity may be extended. Furthermore, authorities will need to consider the incentives for biosimilar companies and evaluate whether some amount of data exclusivity for biosimilars will be necessary to attract investment, especially given that the cost will probably be higher than with generic drugs.

The above recommendations should allow more clarity and predictability for those wishing to enter the market as well as providing enhanced scientific rigour, in the interests of patients.

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I. Introduction

In the past fifteen years, biologic drugs have revolutionised the treatment of many life-threatening and rare illnesses, such as cancer and autoimmune diseases. Biologic drugs (or biologics) refer broadly to substances produced by living cells which are used in the treatment, diagnosis or prevention of diseases.¹ They include a wide range of substances, including genetic material, antibodies and vaccines and work by influencing cellular processes that lead to (or block) a disease or affecting diseased cells themselves. Consequently, biologics are able to move beyond merely treating the symptoms of illnesses – which is what drugs based on new chemical entities (NCEs) generally seek to do – to instead slow the progress of or even prevent disease. They are also highly selective and are familiar to the body, so that they avoid affecting healthy cells and tend to have fewer side effects than synthesised NCE-based drugs.²

As a result, biologics have become attractive treatment options and the size of the market has grown rapidly. Between 1992 and 2007, biologic sales grew six-fold³ and now represent around 20% of global pharmaceutical sales.⁴ The biologic market continues to expand, with over 400 new products in the pipeline.⁵

At the same time, many biologics are facing patent expiration – it is estimated that \$10 billion worth will come off patent by 2010, and an additional \$10 billion by 2015.⁶ Consequently, the ability to introduce follow-on substitutes to original biologics, which are also known as biosimilars, presents many opportunities to both research and generic-based companies. Indeed the field of biosimilars seems to be “breaking” the traditional division between the creation of innovative NCE-based medicines by research-based companies on the one hand, and the copying of these medicines by generic companies on the other hand.

Yet the field of biosimilars also presents some significant challenges – safety, regulatory, legal and economic – which are still being discussed and debated in different forums. Most notable is the fact that, unlike the rather simple and straightforward process of introducing a generic equivalent to an original NCE-based drug, the process of introducing a follow-on equivalent (biosimilar) to an original biological drug is far more complex. Consequently, while generic drugs are sometimes referred to as “carbon copies” of the original drug (based on having the same

¹ National Cancer Institute, “Dictionary of Cancer Terms”, http://nci.nih.gov/templates/db_alpha.aspx?expand=B (Accessed 29 June 2009).

² Novartis, “What are biologics?”, 2009, <http://www.novartis.com/research/biologics/what-are-biologics.shtml> (Accessed 29 June 2009).

³ IMS Health, “IMS Health Reports Global Biotech Sales Grew 12.5 Percent in 2007, Exceeding \$75 Billion” (Press Release and Accompanying Charts), 2009

<http://www.imshealth.com/portal/site/imshealth/menuitem.a46c6d4df3db4b3d88f611019418c22a/?vgnextoid=35b79e392879a110VgnVCM10000ed152ca2RCRD&cpsexcurrchannel=1> (Accessed 29 June 2009).

⁴ IMS Health, “IMS Webinar: Biologics”, 2009

<http://www.imshealth.com/portal/site/imshealth/menuitem.a675781325ce246f7cf6bc429418c22a/?vgnextoid=a0c22e9b65802210VgnVCM10000ed152ca2RCRD&vgnextfmt=default> (Accessed 29 June 2009).

⁵ BIO, “Biotechnology Industry Facts”, 2009, <http://bio.org/speeches/pubs/er/statistics.asp> (Accessed 29 June 2009).

⁶ Insmid, “Follow-on Biologics”, 2008, <http://www.insmed.com/fob.php> (Accessed 4 June 2009).

active substance), a biosimilar does not have the same active ingredient and cannot be referred to as the generic version of the original biological drug.

Accordingly, the purpose of this paper is to examine the various implications and dilemmas that biosimilars raise, particularly with regards to the regulatory framework, public safety, commercial opportunities and intellectual property rights (IPRs). The paper will also investigate how these dilemmas are addressed in practice, taking four of the most relevant regulatory pathways that have been developed for biosimilars as case studies.

This paper takes the following structure. First, it looks at three sets of dilemmas: (1) regulatory and public safety, (2) commercial and (3) intellectual property dilemmas. Second, it examines the biosimilar pathways introduced in the European Union, the World Health Organisation, Canada and the United States and evaluates in particular how these pathways have resolved the safety and IP dilemmas discussed in the first section. Finally, it provides policy considerations for future biosimilar frameworks.

2. Challenges Associated with Biosimilars

2.1 Regulatory and Public Safety Dilemmas

2.1.1 *Creating an Appropriate Regulatory Pathway*

The regulatory pathway used for the approval of biosimilars by regulatory health authorities must address the characteristics of biosimilars that distinguish them from generic drugs, or more broadly, the way in which biologics differ from NCE-based drugs.

NCE-based and biologic drugs mainly differ in nature, size and complexity. NCE-based drugs are chemically synthesised, while biologics are made in living systems. Also, NCE-based drugs are mostly small and generally have well-defined structures and characteristics. This is why it is fairly inexpensive and straightforward to introduce generic substitutes (copies) for these drugs (through reverse engineering) and to predict their activity and safety.⁷ Conversely, although some biologics are more straightforward than others, most are large and heterogeneous molecules. As such, it would prove very difficult, if not impossible, to duplicate them in a predictable way. The active ingredient of the biosimilar may be as close to the original as possible, but factors like the source cell, secondary molecules and the manufacturing process can introduce changes that cause the biosimilar to perform

⁷ Grabowski, H., Cockburn, I., Long, G., Mortimer, R., & Johnson, S. "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions, White Paper", Available on BIO site, 2007, p.12 http://www.bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf (Accessed 4 June 2009).

differently than the original biological drug. In particular, since biologics commonly elicit an immune response in patients (or are “immunogenic”) some of these changes may heighten the intensity of the immune response.⁸

As a result, there seems to be a consensus among different health authorities that the regulatory framework for the review and approval of biosimilars should differ from the existing framework for the approval of generic drugs.

The approval process for generic drugs involves significantly less time and expenditure compared with NCEs. For NCEs, pharmaceutical companies are required to submit data demonstrating that the new drug is effective and safe for human use. This involves a lengthy and costly series of non-clinical and clinical trials,⁹ including studies testing the safety of the drug once it is on the market (“post-marketing studies”). These tests make up most of the price tag for the development of a new drug, which is approximately \$1.32 billion, and can take 10 to 15 years to complete.¹⁰

Generic drugs, on the other hand, face an abbreviated approval process. For instance, in the US this is known as the ANDA¹¹ (abbreviated new drug application) and in the EU, the “Annex I” requirements.¹² Importantly, generic frameworks do not generally require the submission of clinical data. To obtain marketing approval, the company must only submit tests demonstrating that the generic drug is bioequivalent, or that its chemical and biological effects are statistically similar, to the original drug.¹³ The process typically takes only a few years and costs a few million dollars or less.¹⁴ Authorities rely on the registration file of the original drug – the data from clinical trials establishing the drug’s safety and efficacy – to authorise generic applications. Without this kind of reliance and comparison, it would be highly difficult, if not impossible, for generic drugs to obtain marketing approval, given the time and huge costs associated with the creation of a registration file. It is also important to note that different countries, such as the US and the EU as well as many other countries, have also attempted to strike a balance between their intention to allow generic companies to only submit bioequivalence tests (i.e. to rely on the original results of the innovators instead of undertaking their own clinical trials) and the need to protect the proprietary data that is submitted by the innovating company during the course of approving the original drug. Such a framework is known as “data exclusivity” and it is discussed later in the paper.

⁸ Ibid., p.12.

⁹ Clinical trials test the safety and efficacy of a drug in human patients, while non-clinical trials test the drug in a lab or in animals.

¹⁰ PhRMA, “Pharmaceutical Industry Profile 2009”, 2009, Inside cover, <http://www.phrma.org/files/PhRMA%202009%20Profile%20FINAL.pdf> (Accessed 12 June 2009).

¹¹ The ANDA was established by the Drug Price Competition and Patent Term Restoration Act of 1984 (known as the Hatch-Waxman Act) and applies only to drugs licensed under the Federal Food, Drug and Cosmetic (FD&C) Act. However, in the US most biologics are licensed under the Public Health Service Act (PHSA). The biosimilars pathway under development in the US would apply to the PHSA.

¹² See “Annex I” of Directive 2001/83/EC.

¹³ For instance, generic-based companies can measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy, volunteers, compared to the original drug. (FDA, “Abbreviated New Drug Application: Generics”, 2009, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm> See also, EMEA, “Questions and answers on generic medicines”, 2007, <http://www.emea.europa.eu/pdfs/human/pcwp/39390506en.pdf> [Accessed 4 June 2009]).

¹⁴ U.S. Congressional Budget Office, “How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry” (Washington, DC: U.S. Government Printing Office, 1998).

However, it is expected that the biosimilar application will be more complex. For instance, in terms of scientific qualities, biosimilars may appear to be the same as the original biologic. Nevertheless, in order to ensure that the biosimilar is sufficiently similar to the original in terms of its safety and efficacy, companies will probably need to submit some clinical data, particularly data demonstrating the level of immunogenicity.¹⁵

Still, the extent to which the application should differ from the generic application has come under fierce debate, especially in the US. There are four key discussions, which are described below.

2.1.2 *The Safety Issues Inherent in Copying a Biologic*

The first discussion concerns the amount of clinical studies that will be required. Here one can make a distinction between two approaches.

The first approach advocates a framework that is based on the “minimum” need for additional clinical testing of biosimilars. Supporters of this approach tend to assume that the differences between the biosimilar and the original biologic may not be significant enough to justify the demand for additional clinical trials. Concurrently, they argue that the cost and time associated with clinical testing create artificial barriers and thus inhibit the commercial opportunities connected to this field.¹⁶

The second approach advocates a much more robust regulatory framework for the testing and approval of biosimilars, arguing that the clinical and biological difference between a biosimilar and the original biologic may be significant and there is a need for additional clinical tests in order to ensure that the biosimilar will be safe for use.

For its part, the US Food and Drug Administration (FDA) has indicated that biosimilar “legislation should require ... the same high standards for approval as reference biological products”, including “one or more clinical studies”.¹⁷ Indeed, the FDA’s approval of Omnitrope, a follow-on version¹⁸ of recombinant human growth hormone, in 2006 was based on both non-clinical and clinical data, in addition to the submission of bio-equivalence test referring to the original drug, Genotropin. For the several biosimilars authorised so far in Europe based on the EU’s regulatory pathway, regulators (the European Medicines Agency, or EMEA) have required applicants to submit data from some clinical trials as well monitor its safety once it is on the market.¹⁹

¹⁵ Immunogenicity is the extent to which a substance elicits an immune response.

¹⁶ Generic Pharmaceutical Association, “Biogenerics”, 2009, <http://www.gphaonline.org/issues/biogenerics> (Accessed 4 June 2009).

¹⁷ Torti, F. “FDA response to House Subcommittee on Health”, 2008, p.5 http://bio.org/healthcare/followonbkg/20080918_FDA.pdf (Accessed 4 June 2009).

¹⁸ Follow-on drugs are versions of previously approved drugs that are highly similar, but not equivalent, to the original drug. They are approved based in part on the original drug’s data demonstrating its safety and effectiveness, and in part on its own data. In the specific case of Omnitrope, the way in which it was approved is analogous to how biosimilars are expected to be approved, but strictly speaking the FDA does not consider it to be a biosimilar. This is because the original drug, Genotropin, was licensed under the Federal Food, Drug and Cosmetic (FD&C) Act, instead of the Public Health Service Act (PHSA) like most biologics.

¹⁹ Tsang, L. and Kracov, D., “Biosimilars: developments in the EU and US”, *PLC Cross-border Life Sciences Handbook 2008/09*, 2008, p.20.

Therefore, it is apparent that both the FDA and the EMEA consider that at least some clinical testing should be required in the framework, although they both indicate that the exact amount required for a given biosimilar will depend on how well the original biologic is understood, as well as the diseases it treats and its route of administration.²⁰

The second discussion relates to whether health authorities should authorise that a biosimilar is therapeutically equivalent with an original biologic²¹, and therefore can be automatically substituted for that product (i.e. without a physician's consent). Health authorities' characterisation of generic drugs as automatically substitutable for original drugs, as well as health policies encouraging or requiring automatic substitution by pharmacists, has allowed them to acquire market share quickly.²² Thus, some would like to see biosimilars being labelled and treated in the same way.²³

However, because the clinical safety of biologics cannot always be guaranteed, health authorities in several countries are deciding not to make a statement on the substitution or interchangeability of biosimilars.²⁴ For instance, EMEA leaves it to member states to make the determination on interchangeability, if they choose to. However, it recommends that that this determination be left to physicians.²⁵ The FDA has echoed EMEA's recommendation, saying that current technology is not able to determine interchangeability with certainty,²⁶ particularly with regards to immunogenic properties.²⁷ However, in the US, it has been suggested that legislation should include a provision for the FDA to be able to make the decision on interchangeability, once the scientific and technological data reaches a more advanced stage.

It is important to note that the understanding of substitution from a safety perspective should not be confused with substitution from the perspective of reimbursement policy. In this case, the remit of health authorities in determining automatic substitution is in light of safety and not cost-containment.

It should also be noted that even if biosimilars are labelled as interchangeable with original biologics, this may not actually allow biosimilars to grab enough market share to generate the revenue and savings that stakeholders are

²⁰ See Torti (2008). Also see EMEA, "Guidelines on Similar Biological Medicinal Products", 2005, <http://www.emea.europa.eu/pdfs/human/biosimilar/043704en.pdf> (Accessed 4 June 2009).

²¹ Drug products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and have the same level of safety as the original product. (FDA, "Glossary", 2009, <http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#T> [Accessed 11 June 2009]).

²² Federal Trade Commission, "FTC Releases Report on 'Follow-on Biologic Drug Competition'", 2009, <http://www.ftc.gov/opa/2009/06/biologics.shtm> (Accessed 11 June 2009).

²³ House Committee on Energy and Commerce, "Detailed outline of the Promoting Innovations and Access to Life-Saving Medicine Act", 2009, http://energycommerce.house.gov/Press_111/20090311/hr1427_detailedsummary.pdf (Accessed 4 June 2009).

²⁴ For definitions of interchangeability and substitution, see EuropaBio, "EuropaBio and Biosimilar Medicines", 2009, p.13, http://www.europabio.org/Healthcare/documents/biosimilar_factsheet_December_2008.pdf (Accessed 16 September 2009).

²⁵ EMEA, "Questions and Answers on biosimilar medicines", 2008, <http://www.emea.europa.eu/pdfs/human/pcwp/7456206en.pdf> (Accessed 11 June 2009). See also, Tsang and Krakov (2008), p.20.

²⁶ Federal Trade Commission, "Emerging Health Care Issues: Follow-on Biologic Drug Competition", 2009, p.ii, <http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf> (Accessed 11 June 2009).

²⁷ See Torti (2008), p. 4.

hoping for. This is first because not many biosimilars may qualify to be interchangeable with the original biologic. For a biosimilar to be categorised as such, the product and its activity would probably have to be understood and tested to an extremely high standard (including clinical tests). This may entail a considerable cost and only some companies may be able to afford such an investment. Second, a biosimilar that is labelled as interchangeable may still not be substituted for the original biologic in practice. Biologics are often administered under physician supervision in clinics or hospitals (particularly for those delivered via injection into the bloodstream and to high-risk patients, i.e. those with cancer),²⁸ meaning that the onus of the decision to substitute would be placed on physicians and patients, rather than pharmacists. And, given the choice, physicians as well as patients may tend to adhere to the original biologic. Hence, pushing for a regulatory framework that authorises automatic substitution of biosimilars may not actually help expand their market share as much as is speculated.

The interchangeability discussion is also tied to a debate on nomenclature for biosimilars taking place in many forums, including the WHO, EU and US. On the one hand, it is argued that the active ingredient of the biosimilar should hold the same international non-proprietary name (INN)²⁹ as the original biologic, not least because not having the same INN may deter substitution of biosimilars with the original biologic as well as with other biosimilars. However, others say that designating the same INN would be misleading, since the biosimilar is not considered to be the same as the original biologic, and may confuse crucial post-marketing surveillance and encourage switching between biosimilar/biologic products (by health providers as well as pharmacists) without sufficient knowledge. Suggested alternatives to assigning new INNs to biosimilars include using a distinct trade name or batch number for every biosimilar product.³⁰

A fourth, smaller discussion on the safety of biosimilars concerns the development of product-specific guidelines to supplement general biosimilar legislation. Health authorities argue that in light of the complexity and heterogeneity of biologics, legislation should not be the sole guide for marketing approval. Rather, experts should produce tailored requirements for specific products or product classes. This may also help to improve transparency and preclude arbitrary or political decisions. It is also argued that narrowing the guidelines should actually make the marketing application more straightforward.

Some stakeholders argue that this may push back the entry of the first group of biosimilars and complicate the abbreviated pathway. For instance, experts in the US estimate that it will take the FDA around one to two years to develop guidelines after biosimilar legislation is finalised. Indeed, in the EU, which has developed tailored guidelines

²⁸ Grabowski, H., Ridley, D., & Schulman, K. "Entry and Competition in Generic Biologics", 2007, p.23, http://papers.ssrn.com/sol3/papers.cfm?abstract_id=992479 (Accessed 5 June 2009).

²⁹ The INN is assigned to each new active substance by the WHO. Generic drugs have traditionally been assigned the same INN as the reference drug, since the active ingredient of the generic is considered to be an exact copy of the active ingredient of the reference drug. The WHO has determined that INNs should be given to biosimilars in the same way they are given to other biologics, i.e. based on the active ingredient. It adds that for all biologics the assessment of the active ingredient should be consistent and precise. See WHO, "Informal Consultation on International Nonproprietary Names (INN) Policy for Biosimilar Products", 2006, p.12 http://www.who.int/medicines/services/inn/BiosimilarsINN_Report.pdf (Accessed 21 September 2009).

³⁰ Tsang and Kracov (2008), p.20. See also, Torti (2008), p.3.

for several biologics, it took over two years after legislation was finalised for EMEA to release its first set of guidelines (although it released guidelines for four different product classes all at once).³¹

Such issues surrounding the safety of biosimilars continue to be debated and discussed. They are likely to be resolved over time, as greater scientific evidence is accumulated that allows for more accurate assessment of the clinical and therapeutic differences between a biosimilar and original biologic, and as manufacturing and post-marketing standards become more precise.

2.2 Commercial implications

With several biologics already at or near the end of their patent term, the introduction of biosimilars offers a lucrative opportunity to various players in the pharmaceutical industry.

However, in contrast to traditional pharmaceutical markets – in which there is a rather clear divide between research and generic-based markets and between the competitors in each market³² – the biosimilar market is a hybrid of both generic and research-based companies. The players consist of those companies that possess the innovative capability and business models to produce biosimilars.

For example, as discussed above, companies need to have the capacity to undertake and finance clinical trials for the testing and approval of a candidate biosimilar (one study suggests that a single clinical study can cost several million dollars more than the tests required to demonstrate bioequivalence).³³ Biosimilars will probably also require a more extensive manufacturing process and one that will need to be extremely precise and well-documented. Finally, opportunity costs may come into play – for instance, BioGeneriX calculates that development time of a biosimilar could range between five to eight years (one to two years for cell biology, one year for process analysis, two to four years for clinical studies and one year for approval).³⁴ Taking all these together, some experts speculate that biosimilars could cost anywhere from \$2 million to more than \$200 million, with the higher end applicable to products requiring multiple clinical studies and facing high manufacturing costs.³⁵ For the time being, the biosimilar market is small and focuses mainly on a few of the less complex biologics, like human growth hormone (somatropin), filgrastim and erythropoietin products.

³¹ EMEA, “Specific Guidelines for Human Medicinal Products”, 2009, <http://www.emea.europa.eu/htms/human/humanguidelines/multidiscipline.htm> (Accessed 12 June 2009).

³² IMS, “IMS MIDAS New Market Segmentation Feature”, presented at Pharma Israel Annual Conference, 2006.

³³ Grabowski, Ridley and Schulman (2007), p.10.

³⁴ BioGeneriX, “Follow-on Biologics Forum: The Delivery of Regulatory, Legal and Business Strategies Balanced by Scientific Debates”, 2005.

³⁵ Grabowski, Ridley and Schulman (2007). p.11.

However, the next generation of biologics, including gene-derived products and “personalised medicines”, is much more complex. Therefore, producing biosimilar versions of newer biologics in the future will likely be more costly and require greater expertise.

Thus, the existing and future biosimilar players may include both some of the largest generics companies and some research-based companies (depending on several factors, including the state of their pipeline, the compatibility of their business model and their therapeutic focus).³⁶

It should also be noted that, given the relative complexity of creating a biosimilar and the possible absence of automatic substitution, the biologics market may see fewer biosimilar competitors as well as a smaller gap in prices between biosimilars and original. The advent of abbreviated pathways for generic drugs saw the entry of multiple generic competitors and visible gaps in prices between generic and original drugs (some estimates suggest between 30-40% of the original drug price initially and 60-70% within two years of market entry³⁷).³⁸

However, this may not be the case for biosimilars. For example, after two years in the market, three biosimilar versions of erythropoietin (EPO) approved in the EU had attained a combined market share of between 14 to 30% in Germany and were priced at about 25% lower than the price of original EPO products.³⁹ Nonetheless, scope remains for biosimilar entry and some price reduction from original biologics, especially over the medium to long-term.

³⁶ In terms of generic-based companies, Sandoz has gained approval in several countries, including in the EU, US and Canada for Omnitrope, a follow-on version of human growth hormone, as well as for three other biosimilars in the EU. The EU has approved biosimilar versions of G-CSF (a stimulant of white blood cell production) by Israel-based Teva, leading the global generics market, and Germany's Ratiopharm, the largest European generics company, Teva has also partnered with Lonza, a Swiss biotech manufacturer, and acquired two US biotech firms, Barr Pharmaceuticals and CoGenesys. Ranbaxy, the generic-based Indian giant, has agreed to market a local biotech firm, Zenotech's, oncology biosimilar products, beginning in several developing countries. In terms of research-based companies, MerckBioVentures agreed in February 2009 to purchase the follow-on portfolios and facilities from Insmad, a development stage company working primarily with G-CSF. Eli Lilly has also acquired ImClone Systems, a smaller biotech firm, from which it plans to add some follow-on biologics to its portfolio. AstraZeneca has expressed interest in doing the same. In addition, Pfizer has opened the door to a follow-on biologic programme by licensing several products of Aurobindo, an Indian generic-based company. See: Challenger, C. “The biosimilars market continues to grow”, ICIS, 11 March 2009, <http://www.icis.com/Articles/2009/03/16/9199484/the-biosimilars-market-continues-to-grow.html>; Zenotech, “Ranbaxy signs pact with Zenotech for biosimilar product”, 7 February 2007, <http://www.zenotechlabs.com/htmlfiles/biosimilar.htm>; Insmead, “About Us”, 2008, <http://www.insmed.com/about.php>; Jack, A. “AstraZeneca eyes move into 'biosimilars'”, *Financial Times*, 22 December 2008, http://www.ft.com/cms/s/9740a42e-d064-11dd-ae00-000077b07658.Authorised=false.html?_i_location=http%3A%2F%2Fwww.ft.com%2Fcms%2Fs%2F0%2F9740a42e-d064-11dd-ae00-000077b07658.html&_i_referer=http%3A%2F%2Fsearch.ft.com%2Fsearch%3FqueryText%3Dastrazeneca%2Bbiosimilars%26x%3D0%26y%3D0; Reuters UK “Pfizer to license generics from India's Aurobindo”, 3 March 3 2009, <http://uk.reuters.com/article/asiaMergersNews/idUKN0240167220090303?pageNumber=2&virtualBrandChannel=0> (Accessed 30 September 2009).

³⁷ Grabowski, H. “Patents and New Product Development in the Pharmaceutical and Biotechnology Industries”, Duke University, 2002, p.8, <http://www.econ.duke.edu/Papers/Other/Grabowski/Patents.pdf> (Accessed 11 June 2009). See also, Heldman, P. “Follow-On Biologic Market: Initial Lessons and Challenges Ahead at FTC Roundtable: Emerging Healthcare Competition and Consumer Issues”, presented at the *FTC Public Roundtable on Follow-On Biologic Drug Competition*, 2008, <http://www.ftc.gov/bc/workshops/hcbio/docs/fob/pheldman.pdf> (Accessed 11 June 2009).

³⁸ Federal Trade Commission, “Emerging Health Care Issues: Follow-on Biologic Drug Competition” (2009), p.19.

³⁹ Heldman (2008).

2.3 Intellectual property dilemmas

Pharmaceutical IPRs play a crucial role in incentivising the development of innovative medicines. However, biosimilars pose several dilemmas with regards to IPRs, particularly patent protection and data exclusivity.

2.3.1 Patent-related challenges

Biosimilars raise at least two major discussions associated with patents. The first relates to the actual R&D process leading to the creation of a new drug and the second to litigation.

First, the fact that a biosimilar will not be required to be the “same” as the original drug potentially allows biosimilar companies to “design around” relevant patents,⁴⁰ so that they create a product that is (1) sufficiently similar to rely, at least to some extent, on the marketing approval of the original biologic, yet (2) sufficiently different to avoid patent infringement.⁴¹ If this occurred, biosimilars could reach the market well ahead of the expiration of patents belonging to original drugs and with considerably lower expenses, even taking into consideration the additional R&D time that will likely be necessary for biosimilars. As a result, some experts argue that patent protection may not be as robust for biological drugs as it is for NCE-based drugs.⁴²

As will be discussed later in the paper, one proposed solution to address this potential gap in patent protection (which is currently being discussed in the US) is to extend the period of data exclusivity provided to original biologics. On the other hand, a recent report by the Federal Trade Commission (FTC), “Follow-on Biologic Drug Competition”,⁴³ counters this position, arguing that “designing around” is not likely to occur on the most relevant patents (e.g. on the active ingredient) and that other “designing around” is actually positive – it allows for incremental innovations. However, the report seems to overlook the fact that, unlike most biologics competing with the original biologic (“second-in-class biologics”), biosimilars will also be relying on the original drug’s clinical data. As such, the report does not consider whether this will give biosimilar companies an unfair advantage in the market (especially in cases where, like generic drugs, they are viewed as cheaper, and hence more attractive, versions).

⁴⁰ This is viable for biologics because many are protected only by “process” patents, due to current limitations to patenting naturally occurring substances. In addition, the fact that biologics are so much bigger than NCE-based drugs offers biosimilar companies many possible ways of altering a product while still keeping it similar to the original biologic. See, BIO, “A follow-on biologics regime without strong data exclusivity will stifle the development of new medicines”, 2007, p.3, http://www.bio.org/healthcare/followonbkg/FOBSMarket_exclusivity_20070926.pdf (Accessed 30 September 2009).

⁴¹ Taylor, J. “Re: Emerging Health Care Competition and Consumer Issues – Comment, Project No. P083901”, BIO, 2008, p.15, <http://bio.org/healthcare/followonbkg/comments10012008.pdf> (Accessed 10 August 2009).

⁴² Ibid.

⁴³ Federal Trade Commission, “Emerging Health Care Issues: Follow-on Biologic Drug Competition” (2009), pp.36-38.

Second, since a biologic can hold several patents⁴⁴ – not only on items like the active ingredient and route of administration, but also on the development and manufacturing technology, disputes over patent infringement may become even more complicated and costly.⁴⁵ Therefore, it may be in the interest of both sides to streamline the resolution of patent disputes in a manner which is more suitable to the nature of these particular products.⁴⁶ Several debates ensue from this notion, particularly on whether a formal resolution process is needed (in general, this would probably involve the mutual exchange of information and timing constraints) and if it is, on the design of the process.

Proponents of a patent resolution system argue that it would arrange a framework for more straightforward and speedy communication between research and generic-based companies, as well as with third parties (i.e. universities).⁴⁷ On the other hand, critics of this model argue that the costs of a patent resolution process would outweigh the benefits. For example, the FTC's report contends that sharing patent information would actually increase litigation and anti-competitive practices that delay biosimilar entry (i.e. "pay for delay" settlements).⁴⁸ In addition, it argues that biosimilar companies will likely be able to afford to enter the market prior to the end of litigation and will not require the resolution process to speed it up. However, it is important to note that the FTC's report is based on assumptions regarding the extent of biosimilar competition as well as how biologic patents will be managed that have yet to be proven.

The design of the resolution framework itself also elicits several discussions. For instance, in some cases, like one framework under discussion in the US, the onus of patent notification falls on the company that owns the original biologic (at the request of the biosimilar applicant, the patent holder would need to identify a list of patents related to the original biologic, but the biosimilar applicant would not be required to release information about its product).⁴⁹ This arguably gives an unfair information advantage to biosimilar companies. In addition, it is difficult to find the appropriate balance with regards to the timing of patent resolution, i.e. so that litigation does not delay the entry of biosimilars to the market, but at the same time does not cut short the exclusivity of biologics.

⁴⁴ This is primarily due to its complexity and size, as well as a trend toward narrower patents. See BIO, "A follow on biologics regime..." (2007), p.3.

⁴⁵ Taylor (2008), pp. 10-12.

⁴⁶ In the US, NCE-based drugs utilise a framework for patent resolution provided in the Hatch-Waxman Act. The ANDA must identify the patent(s) for which a claim of infringement could be asserted, certifying that it is either invalid or will not be infringed, i.e. the generic drug will not be mass-produced or marketed until after the patent expires. The patent owner(s) then has 45 days to file an infringement suit against the generic company. See FDA, "Paragraph IV Drug Product Applications", 2009, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm147166.htm> (Accessed 4 June 2009).

⁴⁷ House Committee on Energy and Commerce, "Detailed outline of the Promoting Innovations and Access to Life-Saving Medicine Act", (2009), p. 5. See also, Eshoo, A. "Statement of Rep. Anna Eshoo, Introduction of the 'Pathway for Biosimilars Act'", US House of Representatives, 2008, p. 3, <http://www.safeinnovativemedicine.com/pdfs/biosimilars-intro-statement.pdf> (Accessed 10 August 2009).

⁴⁸ Federal Trade Commission, "Emerging Health Care Issues: Follow-on Biologic Drug Competition" (2009), p. 58.

⁴⁹ House Committee on Energy and Commerce, "Detailed outline of the Promoting Innovations and Access to Life-Saving Medicine Act" (2009), pp.4-5.

2.3.2 Data exclusivity challenges

In tandem with patent dilemmas, biosimilars also generate debates on data exclusivity.

Briefly put, data exclusivity is aimed at protecting and safeguarding pharmaceutical registration files – the data submitted by pharmaceutical companies to regulatory authorities, such as the FDA and the EMEA, for the purpose of obtaining marketing approval for new drugs.⁵⁰

Compared with patents, the market power of data exclusivity is, in theory, less restrictive, mainly because it does not legally prevent other companies from generating their own registration data. However, in practice, the vast financial resources and extended time required for gathering and generating pharmaceutical registration data for a new drug create a market barrier that is too high for generics companies to overcome.

The data included in the registration file of a pharmaceutical product is disclosed to the health regulatory authorities; without this data, a drug cannot be approved for market use. In this context, the very idea of data exclusivity is linked to the responsibility and willingness of governments to protect this data.

There are two conceptual and practical layers to this responsibility. The first – non-disclosure – is quite straightforward. Non-disclosure aims to ensure that rival companies (usually generics) do not gain access to the registration file of the original product.

The second layer – non-reliance – aims to prevent the authorities themselves from relying on the registration file of an original drug in order to compare it to the chemical and toxic levels of a potential generic substitute (so-called bio-equivalence tests). The issue of non-reliance is further complicated by the differences between direct and indirect reliance or active and passive reliance.

However, for the purpose of this paper, suffice it to say that the framework of data exclusivity defines the number of years that will elapse before regulatory authorities may review and approve the use of a generic substitute on the basis of the data that was submitted to these authorities by the owner of the original drug. For example, data exclusivity in the United States is provided for by Section 355 of the Federal Food, Drug, and Cosmetic Act of 1997.⁵¹ The US model provides a five-year period of data exclusivity to new drugs and three years of data exclusivity to new indications of existing drugs. In March 2004 the European Parliament harmonised and upgraded

⁵⁰ For a review of data exclusivity see: Pugatch, M. P. "Intellectual property and pharmaceutical data exclusivity in the context of innovation and market access", in: Vivas-Eugui, D., Tansey, G., & Roffe, P. (eds.), *Negotiating Health* (Earthscan & International Centre for Trade and Sustainable Development: Geneva, February 2006); Pugatch, M.P. "Data Exclusivity in the Context of EU Enlargement", *IPR Bulletin*, No. 12, December 2003–January 2004, pp. 10–15.

⁵¹ USFDA, United States Federal Food, Drug, and Cosmetic Act of 1997, Chapter 5, "Drugs and Devices", Section 355, 25 United StatesC. 305(c)(D)(ii) and (iii), www.fda.gov/opacom/laws/fdcact/fdcact5a.htm.

Directive 2001/83/EC in order to provide a data exclusivity period of ten years (or more accurately adopted the “8-plus-2-plus-1” formula: 8 years data exclusivity, 2 years of marketing exclusivity (in which the generic drug may be approved for use by the authorities but cannot be marketed) and an additional year of protection for new indications of existing products).⁵²

In this context, biosimilars raise several discussions on data exclusivity, including discussions on the appropriate length and scope.

The term of data exclusivity for biosimilars

The question of how long the term of data exclusivity should last has proved to be highly polemical, especially in the US. One approach is to maintain the same or similar period as for NCE-based drugs⁵³ in order to get biosimilars into the market as soon as possible. Two major arguments support this approach. First, patent protection is sufficiently long (up to 25 years if an extension occurs) and therefore allows the patent holder to enjoy a meaningful period of exclusivity. Second, biosimilar competition will be subdued compared to past generic competition, and this will allow research-based companies to continue to profit substantially after the exclusivity period of original drugs ends, so that they will not rely primarily on that period to break even.⁵⁴

However, another approach based on different assumptions has been to offer a longer period, between 12 to 14 years. This would be in exchange for two potential scenarios. The first is a case in which there are gaps in patent protection due to designing biosimilars around the original biologic (discussed above). Proponents of a longer term argue that without it, in the event that gaps in patent protection occur, original biologics will not enjoy a suitable term of marketing exclusivity. The impact of this scenario depends on what is considered to be a suitable term of marketing exclusivity for a biologic, which, of course, is an open question.

Nevertheless, some industry figures, such as those of Grabowski, Long and Mortimer, suggest that research-based companies will need a period of between 12 to 16 years⁵⁵ of exclusivity to recoup the full cost of a biologic. This estimate is supported by BIO, the organisation representing the biotechnology industry.⁵⁶

⁵² See Legislative Resolution on the Common Position Adopted by the Council with a View to Adopting a European Parliament and Council Regulation Laying Down Community Procedures for the Authorization and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Medicines Agency, 10949/2/2003–C5-0463/2003–2001/0252(COD), Strasbourg, 17 December 2003, P5_TA-PROV(2003)0577; See also, 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, *Official Journal of the European Communities*, 28 November 2001, L 311/67.

⁵³ The US grants five years of data exclusivity for new drugs, i.e. five years will elapse between the approval of the original drug and the approval of a generic version, and gives an additional three years for new indications, or uses of the original drug that are authorised within three years of the drug's approval (25 USC 355(c)(D)(ii & iii), Federal Food, Drug, and Cosmetic Act of 1997, Chapter 5 - Drugs and Devices, Section 355). The EU affords a total of ten years of exclusivity, eight of data exclusivity, two more of marketing exclusivity (in which generic applications can be approved, but not mass-produced or marketed) and a one year extension for new indications authorised within eight years of the drug's approval (Paragraph 8 of Directive 2004/27/EC).

⁵⁴ Federal Trade Commission, “Emerging Health Care Issues: Follow-on Biologic Drug Competition” (2009), p.vii.

⁵⁵ Grabowski, Long and Mortimer (2008), p. 30.

⁵⁶ Greenwood, J. “BIO Letter of Support for H.R. 1548”, BIO, 2009, <http://bio.org/healthcare/followonbkg/20090317.pdf>. See also Taylor

Based on these figures, some experts and research-based companies are arguing that without a 12-16 year term of data exclusivity or an alternative guarantee against gaps in patent protection, incentives for investing in new drug development could be powerfully undermined.⁵⁷

The second scenario supporting a longer term of data exclusivity is the possibility that drug authorities will need to broaden their reliance on the registration file of original biologics as part of the approval of biosimilars. For instance, when authorities compare clinical data submitted by biosimilar applicants with the clinical data contained in the registration files of original biologics, this could constitute greater reliance on trade secrets belonging to original biologics than has occurred with generic applications. In exchange for allowing greater access to their trade secrets, there is the possibility that original biologic companies should enjoy a longer period of data exclusivity.

The scope of data exclusivity: extending it to include biosimilars?

A final potential dilemma has to do with biosimilars, rather than with original biologics: if biosimilar companies are required to submit clinical data, this data arguably constitutes trade secrets belonging to the biosimilar company. The debate here concerns whether these trade secrets should be protected, like they are for new biologics, and if so, for how long?

However, unlike new biologics, this hypothetical data exclusivity for biosimilars would not guarantee exclusivity in the market, as in theory several biosimilar companies may enter the market roughly at the same time. On the other hand, a framework mimicking the generic pathway in the US – in which the first generic applicant receives six months of marketing exclusivity – is being considered for biosimilars. Proponents of this model argue that, in this way, biosimilars could obtain a degree of exclusivity, albeit only the first biosimilar applicant. However, there are also arguments against giving a marketing exclusivity period to biosimilars, including those presented in the FTC's report, which contends that sufficient incentives exist to encourage the entry of biosimilars without providing them with an exclusivity period.⁵⁸

All told, these potential scenarios have stoked heated debates as to if and how research and generic-based companies should be compensated and incentivised in the context of biosimilars entering the market. However, as explained in the following section, the way that different countries, regions and multilateral organisations address these debates varies.

(2008).

⁵⁷ For example, see "Wyeth Comment to the FTC Roundtable on Follow-On Biologics", 2008, p. 9, cited in Federal Trade Commission, "Emerging Health Care Issues: Follow-on Biologic Drug Competition" (2009), p.41.

⁵⁸ Federal Trade Commission, "Emerging Health Care Issues: Follow-on Biologic Drug Competition" (2009), pp. 55-56.

3. Existing Regulatory Models

A range of countries have regulatory frameworks for approving biosimilars (some of these countries call them “biogenerics”). The EU probably has the most advanced framework in place. Canada’s framework is not yet finalised but is already in use. In addition, regulatory pathways are currently under discussion in both the US and Japan. Furthermore, the World Health Organisation is also in the process of putting global standards in place.

We will discuss some of the most relevant frameworks here and analyse their different approaches, based on two levels:

- (1) The manner in which such frameworks address the issue of safety (for example, whether they require additional clinical data, within reason, for the approval of a biosimilar, requirements for post-marketing safety studies, the standard they employ for interchangeability, etc) and
- (2) The manner in which such frameworks deal with different IP issues (including questions concerning patents and data exclusivity, discussed above).

Generally speaking, it can be noted that like the abbreviated pathway for generic drugs, these frameworks tend to evaluate biosimilars based on how they compare to the original biologic (in terms of quality⁵⁹, safety and efficacy⁶⁰) rather than on their own merit, although this is less true for the two US proposals. In addition, the frameworks tend to determine the necessary clinical studies based on the scientific differences between the biosimilar and the original biologic. This can be said to improve the efficiency of the clinical stage without sacrificing public safety.

3.1 European Union (EU)

The EU is the first major player to develop a regulatory model for biosimilars. Article 10(4) of the EU’s Code for Human Medicines Directive (2001/83/EC) was amended in 2004 (by Directive 2004/27/EC) to authorise the abbreviated approval of biologic products that claim to be similar to an original product. However, the legislation leaves a wide margin of discretion to the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) to develop product class-specific guidelines that determine the extent of non-clinical and clinical testing that will be required. Since 2006, EMA has released guidelines covering several different types of recombinant proteins, including insulin, granulocyte-colony stimulating factor (G-CSF), somatotropin and erythropoietin, as well as low-molecular weight heparins (these will come into effect in October 2009).⁶¹ Up until

⁵⁹Quality refers to the scientific characterisation of the product, in terms of chemical, pharmaceutical and biological data.

⁶⁰ The safety and efficacy of a product are generally demonstrated by the results of non-clinical and clinical studies.

⁶¹ See EMA, “Scientific Guidelines for Human Medicines”, 2009, <http://www.emea.europa.eu/htms/human/humanguidelines/multidiscipline.htm>

now, EMEA has authorised at least thirteen biosimilars, all versions of Somatropin, Epoetin alfa, Epoetin zeta or Filgrastim.⁶²

3.1.1 Safety standards

EMEA's product class-specific guidelines (as well as the primary EU legislation) help set a minimum standard for safety in the approval of biosimilars. They explicitly require the results of preclinical and clinical tests, although they vary as to the extent of testing – in the case of somatropin, the guideline recommends at least one clinical trial, while for erythropoietins at least two are required.⁶³ EMEA has also introduced special guidelines for immunogenicity assessments and for cases in which changes are made to the manufacturing process after approval has taken place. Furthermore, all the products authorised thus far are subject to post-marketing safety monitoring.⁶⁴ As mentioned earlier, regarding whether a biosimilar is interchangeable or automatically substitutable, although the decision is a national competency, EMEA has stated that biosimilars cannot be considered identical to original biologics. Accordingly, fifteen member states have either banned automatic substitution of biosimilars for original biologics (i.e. UK, Germany, Sweden, Spain and the Netherlands) or require the physician to prescribe by brand name (i.e. Greece, Austria, Czech Republic).⁶⁵ The standard for using the same INN as the reference biologic remains unclear at the European level. Biosimilars are required to have a distinct trade name, but do not need a different INN.⁶⁶ As a result, in practice some biosimilars use the reference drug's INN, while others do not.

3.1.2 Intellectual property standards

The EU applies the “8+2+1” formula of data exclusivity which was adopted in 2004. As explained before, according to this formula new pharmaceutical products would be entitled to eight years of data exclusivity, two years of marketing exclusivity (in which generic companies would be allowed to submit bio-equivalence tests) and an additional year of protection for new indications of existing products.⁶⁷ This formula affords a period closer to the 12 to 14 year period suggested for biologics earlier. Nevertheless, the EU has not yet addressed whether biologics

(Accessed 5 June 2009).

⁶² Perry, G. “Biosimilar Medicines: Towards Global Development and Monoclonal Antibodies”, presented at the 7th EGA Annual Symposium on Biosimilar Medicines, EGA, 2009, http://www.egagenerics.com/doc/ega_biosimilars09_perry.pdf (Accessed 4 June 2009).

⁶³ Tsang and Kracov (2008), p. 19.

⁶⁴ Ibid., p. 20.

⁶⁵ Morgan Stanley, “Follow-on Biologics: Expect a slow start”, 2008 cited in Taylor (2008), p.3. It should be noted that in the case of Sweden, in some instances the policy on automatic substitution is not clear cut (i.e. as to whether authorised biologic substitutes are parallel imports or biosimilars, see also Sweden's Medical Products Agency, “List of Substitutable Products”, 18/9/09, http://www.lakemedelsverket.se/upload/halso-och-sjukvard/forskrivning/utbytbarhet/gk_utbytbara%20grupper%20internet.pdf), though as a general rule, automatic substitutions occur based on the same active ingredient. See Sweden's Medical Products Agency, “Biosimilars' are not deemed to be interchangeable”, 2007, <http://www.lakemedelsverket.se/malgrupp/Halso---sjukvard/Artikelsamlingar/Lista/Lakemedelsformanerna-och-utbytbarhet/Biosimilars-bedoms-inte-vara-utbytbara/>.

⁶⁶ Tsang and Kracov (2008), p.20. See also, Taylor (2008).

⁶⁷ For a longer discussion on this formula see, Pugatch (2006).

merit a separate formula, i.e. a longer term, due to authorities expanding their reliance on the reference file and/or gaps in patent protection. The EU has also not dealt with the idea of affording any exclusivity to biosimilar products. Furthermore, a European-level patent resolution framework is not in place for NCE-based drugs or biologics, since both patents issued at the EU level and those issued at the national level are subject to national laws – with no single Community patent at this time, there is no ground for European-level coordination of patent disclosure.⁶⁸ However, the European Commission recognises in its recent inquiry into the pharmaceutical sector⁶⁹ that the lack of European-wide jurisdiction has made patent dispute resolution in Europe costly and inefficient, and both the Commission and the Council are currently taking steps toward a unified patent litigation system.⁷⁰

Due to its high standards in safety and data protection, the EU/EMA regulatory framework provides a fairly strong model for other countries. However, while this does not necessarily weaken the framework itself, the fact that it does not cover legal issues or address some debates (e.g. related to patent disputes and the question of data exclusivity for biosimilars) that are controversial elsewhere may perhaps weaken its applicability to other countries.

3.2 World Health Organisation (WHO)

WHO has developed a framework of general principles as part of its “Biological Standardisation Process” that seeks to govern the scientific aspects of biosimilars approval.⁷¹ WHO plans to finalise it this autumn following a public consultation.

To aid in the standardisation process, WHO defines a biosimilar, which it labels a “similar biological product” (SBP), as a “biotherapeutic product claimed to be ‘similar’ in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product (RBP), which must have been licensed by national regulatory authorities on the basis of a full registration dossier”.⁷² However, WHO emphasises that its framework is generalised and will only apply to well-established biologics.

The WHO framework strengthens the argument for high standards of safety based on scientific rationale. Specifically, it seeks to rationalise clinical requirements, but recognises that at least one clinical study will be

⁶⁸ EUROPA, “EUROPA Glossary”, 2009, http://europa.eu/scadplus/glossary/community_patent_en.htm (Accessed 5 June 2009).

⁶⁹ DG Competition, European Commission, “Pharmaceutical Sector Inquiry, Preliminary Report”, Executive Summary, 2008, pp. 4, 8, http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/exec_summary_en.pdf (Accessed 2 June 2009).

⁷⁰ EUROPA, “Patents: Commission sets out next steps for creation of unified patent litigation system”, 2009, <http://europa.eu/rapid/pressReleasesAction.do?reference=IP/09/460&type=HTML&aged=0&language=EN&guiLanguage=fr>. See also, European Council, “Preparation of the Competitiveness Council of 28-29 May 2009, Progress Report”, 2009, http://register.consilium.europa.eu/pdf/en/09/st09/st09549_en09.pdf (Accessed 2 June 2009).

⁷¹ Kang, H.N. “WHO Guideline on Evaluation of Similar Biotherapeutic Products: The Next Steps”, presented at the EGA 7th Symposium on Biosimilar Medicines, 2009,

⁷² Ibid.

necessary for a biosimilar to be approved, especially to test its immunogenicity.⁷³ Also, WHO requires that biosimilar applicants include a plan for post-marketing safety assessments in the application for marketing approval.

However, WHO does not address some important debates, namely those regarding interchangeability and intellectual property, since these are not within its mandate as an advisory body. On interchangeability, though, one might infer WHO's position by looking at its emphasis on the idea of "similarity", and not "equivalence", between the biosimilar and original biologic.

3.3 Canada

Canada is also in the process of finalising regulation that allows the authorisation of biosimilars, which it calls "subsequent entry biologics" (SEBs), under the Food and Drugs Act. Although the regulation has not yet been finalised the first biosimilar, Omnitrope, has already been approved.⁷⁴ Like WHO, Canada's approach in terms of safety reflects that of EMEA, but goes beyond EMEA in addressing intellectual property debates.

Notable to Canada's biosimilar framework is its flexibility in the biosimilar applicant's choice of which original biologic it uses as its reference; unlike the other major frameworks, the original biologic may be one that has not been approved and marketed in Canada. This approach has been offered in order that the small size of the biologics market in Canada might not deter biosimilar applicants. However, Health Canada (Canada's department of health) recommends utilising those original biologics that have been approved by jurisdictions with which it has "an established relationship".

3.3.1 *Safety standards*

Health Canada requires "comparative clinical trials ... to demonstrate the similarity in efficacy and safety profiles between the SEB and reference biologic".⁷⁵ However, like the EMEA and WHO guidelines, the amount of clinical testing will be based on how the biosimilar and original biologic differ scientifically. It is not yet clear what this will look like in practice, with Omnitrope as the only example (its application involved the results of at least one clinical trial).

Also, a post-marketing safety strategy, the "Risk Management Plan", is required as part of the biosimilar application, and "Periodic Safety Update Reporting" will also be mandatory. Regarding interchangeability, Health Canada will

⁷³ Kang (2009).

⁷⁴ Sandoz, "Sandoz Canada receives approval for recombinant human-growth hormone Omnitrope, the first Subsequent Entry Biologic in Canada", 2009, http://www.sandoz.ca/site/en/company/news/news_releases/pool/20090422-EN-Press_release_Omnitrope.pdf (Accessed 1 June 2009).

⁷⁵ Nyarko, K.A. "Regulatory Approach for Subsequent Entry Biologics in Canada", Health Canada, presented at the PMDA 3rd International Symposium on Biologics, 2009, [http://www.pmda.go.jp/2009bio-sympo/file/IV-2_Nyarko_\(Health%20Canada\).pdf](http://www.pmda.go.jp/2009bio-sympo/file/IV-2_Nyarko_(Health%20Canada).pdf) (Accessed 4 June 2009).

not take the decision; it is to be taken at the provincial level. Although in this sense, Health Canada is institutionally similar to EMEA, it takes a somewhat different policy approach. In particular, there is no explicit statement that a biosimilar cannot be considered identical to the original biologic. Rather, Health Canada emphasises that (1) its authorisation of a biosimilar does not indicate that the product may be automatically substituted with the original; and (2) if a body is to make a decision on interchangeability, this should be based on appropriate scientific and clinical data.

3.3.2 IP standards

Canada's guidelines apply the same data exclusivity to original biologics as that given to NCE-based drugs: eight years, with no filing of a generic application for six years.⁷⁶ In addition, the arrangement for patent dispute resolution in place for generic drugs will be applied to biosimilars, which involves the biosimilar applicant communicating the relevant patents to the patent holders and an opportunity for the original drug's manufacturers to respond.⁷⁷

Overall, Canada's biosimilar framework sets moderately high safety and IP standards, although the fact that the original product need not be approved in Canada could compromise Health Canada's ability to fully assess the safety of the biosimilar. In addition, in applying the same IP and legal framework to biologics and NCE-based drugs, the guidelines do not address the dilemmas discussed earlier. In particular, like the EU, Canada's guidelines do not give additional data exclusivity to original biologics or provide exclusivity to biosimilars. Also they do not tailor a dispute framework to the complexities of biosimilars.

3.4 United States (US)

Reflective of how complex the debate has been in the US, in the last Congress five proposals for an abbreviated biologics pathway⁷⁸ were introduced, but were never fully debated. Of the three bills introduced in the current Congress, two are companion bills in the House and the Senate (H.R. 1427 and S. 726), introduced by Representative Waxman (D-CA) and Senator Schumer (D-NY) respectively as slightly modified versions of a previous proposal. The third is the proposal Representative Eshoo (D-CA) has reintroduced from the last Congress (now H.R. 1548). The approaches of the Waxman/Schumer and Eshoo proposals in addressing the challenges presented by biosimilars differ considerably, especially on safety and IP issues.

⁷⁶ This measure (introduced in a 2006 amendment to the Food and Drug Act) restricts drug authorities from relying on data of the original drug for generic drug approval prior to the expiration of the original drug's patent(s).

⁷⁷ Health Canada Office of Patented Medicines and Liaison, "Guidance Document: Patented Medicines (Notice of Compliance) Regulations", 2009, http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/patmedbrev/pmreg3_mbreg3-eng.php#1 (Accessed 2 June 2009).

⁷⁸ This will apply to biologics licensed under the Public Health Service Act (which covers most biologics).

It is important to note that the approaches under consideration here are legislative frameworks – the so-called “bare bones” of what will become the US pathway. The “meat” of the pathway will come as the FDA adds specific guidance (although it is not clear how extensive this will be), which should likely make the approach to safety more concrete.

3.4.1 *Safety standards*

The Waxman/Schumer proposal is vaguer on the basic safety standards required for approval and on how much capacity it will give the FDA to set these standards, particularly product-specific requirements. This is true for clinical testing in general, but particularly for testing of immunogenicity.

On the other hand, the Eshoo proposal requires both non-clinical and clinical studies and while it allows the FDA to waive them if it judges them unnecessary, it may only do so if it has published highly specific guidelines on immunogenicity.

However, neither bill seems to employ comparability exercises (evaluating the scientific differences between the original and biosimilar drug) to determine the amount of clinical studies necessary. In this way, the Eshoo bill risks requiring an excessive amount of clinical testing, and the Waxman/Schumer bill an insufficient amount.

Both bills do require post-marketing safety studies, to the same level as is required of original biologics.

Another key break with the other frameworks is that both proposals allow the FDA to state (in a separate decision from approval) that a biosimilar is automatically substitutable for the original biologic. This comes despite the fact that the FDA itself has been leery of possessing this competency, as well as the idea that institutionally-speaking, the FDA could take a similar approach to Health Canada and leave the decision to state policy. However, major influences are at work here, including the view that the approach for chemical entities – in which the FDA indicates their therapeutic equivalence in the “Orange Book” and many states then use this as a reference for generic substitution policies – can apply to biologic products as well.

Providing that the FDA is authorised to make the decision on interchangeability, the Eshoo would only allow it to do so if the biosimilar applicant can produce clinical data (based on FDA guidelines) which indicates that the biosimilar “can be expected to produce the same clinical result as the reference product in any given patient for each condition of use prescribed”.⁷⁹

⁷⁹ H.R. 1548 (112th Congress), Title I (a)(4)(A)(i)(II).

Although the Waxman/Schumer bill is somewhat similar, its approach towards the issue of substitution is more lax. First, it does not require that the FDA create product-specific guidelines on automatic substitution. Second, it mandates that the FDA label a product that may be automatically substituted as interchangeable, in order to encourage its uptake. Third, its authors acknowledge that the bill seeks to incentivise the development of interchangeable products with the idea that they would generate the greatest cost savings.

Altogether, when it comes to the issue of interchangeability, it would seem that the Waxman/Schumer bill is more focused on the issue of potential savings from the introduction of biosimilars (which according to their view may be cheaper than the original biologic) and therefore advocates the principle of “automatic” interchangeability. On the other hand, the Eshoo bill recognises that there may be cases in which interchangeability is appropriate, but only after rigorous comparison between the biosimilar and original biologic at the clinical level.

Finally, both bills leave room for the FDA to manage the nomenclature of biosimilars. However, the Waxman/Schumer bill encourages the use of the INN of the reference biologic as the “official name” of the biosimilar, while the Eshoo bill requires the FDA to assign the biosimilar a name that is unique and “distinguishes it from the reference product”.

3.4.2 IP standards

The two proposals also diverge on IP standards, although they both confront some of the IP dilemmas presented by biosimilars.

On data exclusivity, the Waxman/Schumer bill effectively gives original biologics the same period as for NCE-based drugs – essentially five years of data exclusivity. The Waxman/Schumer bill allows for up to one extra year if it is demonstrated that the biologic can be used to treat a different condition (known as a new “indication”) or pediatric patients. Its proponents base this formula on the idea that biologics should not require more time or expense than NCE-based drugs.⁸⁰ Here it should be noted that current US law [USC (355) c(D)iii & iv] currently allows for three years of exclusivity for new indications of NCE-based drugs.⁸¹ Therefore, the Waxman/Schumer

⁸⁰ House Committee on Energy and Commerce, “Q’s and A’s on the ‘Promoting Innovation and Access to Life-Saving Medicine Act’”, 2009, http://energycommerce.house.gov/Press_111/20090311/hr1427_detailedsummary.pdf (Accessed 16 April 2009).

⁸¹ According to USC (355) c(D)iii & iv: “If an application submitted under subsection (b) of this section for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b) of this section, is approved after September 24, 1984, and if such application contains reports of new clinical investigations (other than bio-availability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) of this section for such drug. If a supplement to an application approved under subsection (b) of this section is approved after September 24, 1984, and the supplement contains reports of new clinical investigations (other than bio-availability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) of this section.”

bill seems to provide a framework for biosimilars which would be lower than the level of data exclusivity protection that is currently being granted to NCE-based drugs in the US.

In contrast, the Eshoo bill gives biologics 12 years of data exclusivity, and an additional two years for new indications.^{82,83} It appears to shore up protection based on the idea that gaps in patent protection for biologics may arise (as discussed above).

It should be noted that there is no mention of lengthening the data exclusivity term for the purpose of compensating the original biologic for greater reliance by drug authorities on its safety data. This may be fitting, because both bills appear to require less comparative testing than the EU/EMA, WHO and Canadian frameworks. Instead, while the biosimilar must be “highly similar to the reference product” at the scientific level, the two US bills seem to evaluate the safety and efficacy of the biosimilar more on its own merit.

Both bills address the debate on compensating biosimilar companies, albeit in a limited way. They do so by offering a period of marketing exclusivity for the first “interchangeable” biosimilar – the Eshoo bill provides two years and the Waxman/Schumer bill six months to one and a half years, in the case of ongoing litigation. However, this can be viewed as only weakly rewarding biosimilars for the data they must generate (compared to generic drugs), especially since it only applies to those that are most similar to the original biologic.

Finally, both proposals include a framework for patent dispute resolution geared towards biosimilars, with broader communication and additional timing constraints. However, each framework takes a different track. The Waxman/Schumer bill requires the patent holder to disclose all relevant patents, but does not require the biosimilar applicant to unveil the details of its applications. This gives an unfair information advantage to the biosimilar applicant. On the other hand, while the Eshoo bill calls for reciprocal disclosure of patent information, it does not impose penalties for failure to comply with the framework.

To sum up, the disparities between the two proposals highlight the different interests playing into both of them. The Waxman/Schumer proposal tends to focus more on the potential public savings that may derive from the introduction of biosimilars (though as discussed above, currently it is not at all clear whether the price reductions that will derive from the introduction of biosimilars are comparable to the existing generic model). The Eshoo bill, on the other hand, is more focused on safety issues as well as on the need to reward innovators for the time and resources invested in the development of the original biological drugs.

It should be noted that recently a pathway for the approval of biosimilars has made its way into two of the health reform bills that have been approved by the Senate and House committees respectively.⁸⁴ The Senate bill comes

⁸² H.R. 1548, 111th Congress, 1st session

⁸³ Both bills also afford an additional six months for conducting paediatric studies. The Eshoo bill offers two years of marketing exclusivity to the first interchangeable biosimilar for a reference product, while the Waxman/Schumer bill gives one year.

from the health (HELP) committee and the House bill comes jointly from three committees (the section on biosimilars is handled by the version done by the Energy and Commerce Committee, headed by Rep. Waxman). The biosimilar pathway included in both bills seems to draw from the Eshoo proposal, as well as from a bill introduced in the last Congress by the late Senator Kennedy.⁸⁵ Importantly, the standard for clinical requirements seems to have dipped slightly, with some flexibility inserted as to the possibility of waiving clinical trials. However, in general, the other issues addressed seem to fall in line with the Eshoo approach, with particular emphasis on a 12 year period of data exclusivity.

Although it appears that a biosimilar pathway will likely be included in the final version of a US health reform bill (with the caveat that the future of a health reform bill itself is by no means certain at the time of writing), the details of the pathway are not settled. First, both the Senate HELP bill and the Energy and Commerce version of the House bill will need to be melded with other existing health reform bills, namely the Senate Finance Committee's bill and the two other House versions done by the Ways and Means and the Education and Labour Committees. These bills do not actually address the issue of biosimilars; the pivotal issue here is that the biosimilars pathway existing in the HELP and Energy and Commerce bills remain in the final House and Senate bills. Second, the resulting House and Senate approaches will need to come together into one bill and agreed on both floors. Therefore, it still remains to be seen exactly which direction the final US legislation will take on the safety and IP issues associated with biosimilars.

Table I summarises the different models that have been surveyed in this section.

⁸⁴ See: H.R. 3200, "America's Affordable Health Choices Act of 2009", US House of Representatives, http://energycommerce.house.gov/Press_111/20090311/hr1427.pdf, as well as the subsequent amendment on biosimilars (available at http://energycommerce.house.gov/Press_111/20090731/hr3200_eshoo_2.pdf). See also, S.R.325, "Affordable Health Choices Act", US Senate, http://help.senate.gov/BAI09150_xml.pdf.

⁸⁵ S.1695, "Biologics Price Competition and Innovation Act of 2007", US Senate, <http://thomas.loc.gov/cgi-bin/bdquery/z?d110:s1695>; (Accessed 21 September 2009).

Table I Evaluating existing regulatory pathways

Criteria	EU/EMA	WHO	Health Canada	US H.R. 1427/ S.726	US H.R. 1548
Comparability exercise	Yes	Yes	Yes, with limitation of using reference drugs not yet approved in Canada	No	Yes
Extent of clinical data	Strong	Strong	Strong	Weak	Strong
Post-marketing safety studies	Yes	Yes	Yes	Yes	Yes
Standard and criteria for interchangeability	National decision (EMA recommends decision by physician)	None	Provincial decision	Present, but weak	Present, strong
Data exclusivity	Unchanged from conventional term 8+2+1 formula	None	Unchanged from conventional 8 years with 6 year no-filing period	Unchanged from conventional 5+3 term	12 years of data exclusivity + 2 years for new indications)
Patent dispute resolution framework	None, occurs at national level	None	Allows for mutual exchange of information	Favours biosimilar applicants	Favours owners of the original biologic

4. Conclusions and Policy Considerations

The entry of biosimilars presents several unique policy dilemmas. Forming a pathway for approval that addresses the safety and IP challenges has shown to be a thorny process, particularly when political and commercial interests come into play, as they have in the US.

In order to ensure public safety and to preserve sufficient incentives for future biomedical innovation, the best practices gleaned from existing pathways demonstrate that approval pathways for biosimilars should seek to uphold the following five principles.

- (1) Legislation should require a baseline scientific evaluation of the original drug and the biosimilar. This assessment should establish that key similarities exist between the two (for example, in the active substance, pharmaceutical form, strength and route of administration) and then determine any differences.

- (2) Following on from the first, the legislation should identify the level of clinical data that will be needed to evaluate and approve the biosimilar. This requirement should be twofold. First, product class-specific guidelines should identify a baseline level of clinical testing for various product types. This should take into account the level of existing knowledge about the original biologic and the illness the medicine seeks to treat. Second, the legislation should mandate that more specific clinical requirements be determined based on the differences identified in the scientific comparison with the original biologic described above (for instance, related to the host cell, secondary agents and the development and manufacturing process).
- (3) Legislation should call for post-marketing safety studies in order to monitor any potential differences in safety and efficacy between the biosimilar and original drug that become apparent once a biosimilar enters the market. This should take into account any health-related issues identified during the development stage (i.e. related to differences in quality between the biosimilar and original drug or the manufacturing process), as well health elements that are associated with the original biologic.
- (4) Legislation should define the standard and criteria for interchangeability of the biosimilar with the original drug. The legislation should clarify if marketing approval indicates that automatic substitution is permissible (from a pharmacological, as opposed to a reimbursement/cost containment point of view), or if the decision on substitution should be left to more immediate health authorities or physicians. If central health authorities are given a mandate to determine interchangeability, the legislation should also fix the criteria they should use. The criteria should be well-defined – it should require that the biosimilar produce the same clinical effect as the original drug – and should be tailored to product classes or even individual products. Furthermore, it should prioritise public safety considerations over cost-containment objectives.
- (5) Legislation should provide sufficient incentives to research-based companies via IP protection. It should ensure that patent protection is not eroded with the entry of biosimilars. Importantly, it should recognise the possibility that gaps in patent protection could result from biosimilars designing around patents of the original drug. One way of resolving this is by extending the term of data exclusivity to cover fully or in part the potential gaps. Whatever the data exclusivity term that is deemed appropriate by individual countries, it should as much as is possible, within reason, attempt to off-set the disincentives to investment resulting from potential weakening of patent protection. Legislation should also prevent the erosion of patent protection by making certain that a patent resolution system does not involve asymmetrical patent disclosure (i.e. only by the patent holder). In addition, policymakers should consider to what extent drug authorities will increase their reliance on data belonging to the original drug in order to evaluate biosimilars, as well as the extent to which this may dampen the incentives to develop new drugs. If appropriate, the term of data exclusivity can be extended accordingly. Furthermore, authorities will need to consider the incentives for biosimilar companies and evaluate whether some amount of data

exclusivity for biosimilars will be necessary to attract investment, especially given that the cost will probably be higher than with generic drugs.

Biosimilars present considerable opportunities – whether for growth in the healthcare sector or for treating patients – especially over the long-term. Concurrently, however, policymakers must ensure that high standards of public safety are maintained to protect patients and that the right IP framework is in place to incentivise innovators. If so, then we can reasonably expect favourable results from the greater use of biosimilars improving healthcare standards in both the developed and developing world.