Biosimilar and Biobetter Scenarios for the US and Europe: What Should We Expect?

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Introduction and Background

FDA-approved biologics have been marketed in the US for more than 30 years (human insulin was the first recombinant therapeutic approved by the FDA in 1982).[1] In spite of this considerable history, the pathway to follow-on biologics (dubbed "biosimilars" by some observers) subsequent to originator loss of patent protection or other exclusivity has only recently begun to evolve, albeit at a more rapid pace in Europe than in the U.S. In this manuscript we discuss how biosimilar development, regulatory approval, manufacturing, branding and marketing, distribution, utilization, pricing and cost savings will differ from the historical experiences of generic small molecules, chemically synthesized therapies, both in the U.S. and Europe. We will also address how and why the European biosimilar diffusion process will likely differ from that in the U.S.

We begin by overviewing the stylized facts and existing literature concerning the evolution of U.S. and European generic small molecule markets, and then review the smaller but rapidly growing body of literature concerning U.S. and European markets for biosimilars and other specialty drugs. Finally, we explore the financial incentives that may drive development of biobetter vs. biosimilar therapeutics.

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[1] Trusheim et al. (2010).

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Stylized Facts of U.S. Generic Small Molecule Market Evolution

The seminal legislation governing generic entry of small molecules into the U.S. market is the 1984 Hatch-Waxman Act. Rather than requiring duplicative clinical studies demonstrating safety and efficacy, this legislation facilitated more rapid and less costly generic entry by only requiring the abbreviated New Drug Application (ANDA) applicant to demonstrate bioequivalence to the innovator drug, as well as compliance with current good manufacturing practices (cGMP). If the innovator's patents are not successfully challenged, typically relatively unfettered and massive generic entry now occurs on the day of loss of exclusivity (LOE), with the number of entrants depending in large part on the dollar or prescription volume of pre-LOE sales, and/or on the complexity the manufacturing or use of the drug entails.[2] Although generally increasing over time since passage of the Hatch-Waxman legislation, the generic efficiency rate (for molecules having multisource entry following LOE, the proportion of brand plus generic scripts dispensed as generics) has exceeded 90 % in the U.S. retail market in recent years, approaching its theoretical limit of 100 %, and has done so increasingly rapidly—on average over all small molecules, within 3–4 months of LOE the generic penetration rate (the proportion of all prescriptions dispensed as generic) now approaches 80–90 %.[3] Though not utilized initially for more than a decade, the legislation also provided incentives for generics to challenge innovators' patents as being invalid or not infringed by the ANDA applicant; the successful first-to-file ANDA Paragraph IV challenger is rewarded by being given 180 days of exclusivity, during which time no other ANDA holder can market the drug formulation/strength. However, brands can enter under their original New Drug Application (NDA) during the 180-day exclusivity period, launching their authorized generic (AG) to compete in a triopoly setting with the

[2] Grabowski et al. (2011) define a complex small molecule as one meeting two or more of the following criteria: black box warning, narrow therapeutic index, prescribed by specialists, oncology products, or manufacturing technology that is available to only a limited number of firms. The more complex the drug, *ceteris paribus*, the fewer the number of generic entrants at the time of LOE. Olson and Wendling (2013) find that entry both during and after the 180-day exclusivity depends not only on pre-LOE market size, but also is greater if the drug at issue was originally designated a New Chemical Entity (NCE) by the Food and Drug Administration during the NDA approval process.

[3] IMS Institute for Healthcare Informatics (2011a), p. 21, and Aitken et al. (2013). Earlier studies include those by Hurwitz and Caves (1988), Ellison et al. (1997), Cook (1998), Reiffen and Ward (2005), Saha et al. (2006), Aitken et al. (2008), Aitken and Berndt (2011), Berndt and Aitken (2011) and Berndt and Newhouse (2012). Regarding complexity, as discussed in the previous endnote, Grabowski et al. (2011, pp. 540–541) report that "On average, drugs with two or more characteristics faced 2.5 geneic entrants 1 year following initial generic entry, while drugs with one or no complexity characteristics faced an average of 8.5 entrants." Mean generic share of non-complex small molecules was 1.7 times larger than for complex small molecules, while the mean price discount from brand price was 1.6 times larger (price here reflecting manufacturer's revenues from sales to wholesalers and direct customers).

entrants consisting of the possibly cannibalized own brand, the successful first-to-file Paragraph IV challenger, and the authorized generic.[4]

In the case of a triopoly during 180-day exclusivity, at the retail level average prices for the ANDA and the AG are about 20 % less than the brand, although pharmacy acquisition prices (and hence, average revenues to the ANDA and AG manufacturers) are discounted even more, implying that during the 180-day exclusivity retail margins are very substantial.[5] In spite of this modest retail price reduction during the 180-day exclusivity, early evidence suggested that within 4 weeks of LOE, the volume share of the combined successful ANDA challenger plus the AG was about 75 %.[6] Since the choice of who will be the AG is a decision made by the brand seeking to maximize its post-LOE profits (the AG could be an independent generic firm licensed to market the AG while paying the brand a royalty for the privilege, or a generic subsidiary of the brand), the more interesting combined share is that of the brand and the AG, particularly since according to the Federal Trade Commission (2011, p. 85), in recent years the royalty rate paid the brand by the AG has been in excess of 90 %. Evidence from the 2009–2013 time frame in the U.S. suggests that during the 180-day exclusivity, the brand volume share ranges from about 15 to almost 50 %, and the AG share from 20 to 30 %, with the combined brand plus AG share ranging between 50 and 65 %, while that for the successful first-to-file ANDA challenger is between 35 and 50 %.[7] To date, sample sizes in studies analyzing AG pricing patterns have been too small to detect whether pricing during the 180-day exclusivity differs depending on whether the AG is marketed by an independent generic or a subsidiary of the brand. The evidence does, however, suggest that the presence of an 180-day exclusivity period with restricted entry (either duopoly or triopoly) has no long-term effect on the extent of generic entry post-180-day exclusivity.[8] Notably, in recent years almost all brands at risk for initial LOE have faced patent challenges; these challenges have increasingly occurred at precisely 4 years following initial NDA approval which is the earliest time from initial NDA approval at which the brand's patent can be challenged. In most cases when there is a successful Paragraph IV challenger, the brand has responded with AG entry, although in some settlement situations generic entry has been delayed, or the brand agrees not to launch an AG.[9]

For many years conventional wisdom held that total molecule (brand plus all generic) utilization generally declined following LOE. This post-LOE decline has

[4] If multiple Paragraph IV filers submit their challenge on the same day, the various challengers share the 180-day exclusivity, resulting in a larger number of competitors. See Federal Trade Commission (2011, especially Chap. 7) for more details.

[5] See Federal Trade Commission (2002, 2011), and Aitken et al. (2013) for further details.

[6] Berndt et al. (2007). Also see Branstetter et al. (2011) for estimated effects of Paragraph IV entry on consumers' welfare in the U.S.

[7] Aitken et al. (2013).

[8] Berndt et al. (2007); Federal Trade Commission (2011); Aitken et al. (2013).

[9] Federal Trade Commission (2011, Chaps. 2 and 7, Aitken et al. (2013), Grabowski et al. (2014), and Drake et al. (2014).

been thought to reflect reduced marketing efforts by the brand as LOE approached and after it arrived, attempts by the brand to switch Rx-only to an over the counter version or to its next generation product in the same therapeutic class, as well as an absence of product differentiation marketing competition by generic manufacturers following LOE. However, in recent years a new phenomenon has emerged by which cross-molecule substitution from a patent protected brand to a generic version of another molecule results in total utilization of the off-patent generic molecule increasing following the brand's LOE. This occurred in 2006–2007 when Zocor (simvastatin) went off patent, inducing efforts by payers and their pharmaceutical benefit manager (PBM) agents to incent substitution toward simvastatin and away from the branded more costly Lipitor.[10] More recent data suggest the Zocor-simvastatin-Lipitor increase in post-LOE sales was not unique historically, and instead may become the norm as payers and their PBMs increasingly exercise their ability to effect cross-molecule substitution. Specifically, as reported in Aitken et al. (2013), among the top 50 prescribed molecules in 2013, for four of the six molecules experiencing initial LOE between 2009 and 2013, total utilization post-LOE increased, for one molecule it was relatively stable, and for only one molecule decrease in post-LOE utilization occurred, and that was only a very slight decrease.

In terms of number of generic entrants post-LOE, due to a combination of consolidation M&A activity among generic manufacturers and actual product exit, the total number of generic entrants in the US has tended to peak between 30 and 36 months following LOE.[11] In aggregate, over all products in 2009 the generic penetration rate (the proportion of all retail prescriptions dispensed as generics) was about 80 %, the unbranded generic revenue share was 10–15 % of total revenues, while branded products captured 75 % of revenues, with branded generics obtaining 10–15 % of total revenues.[12] By 2013 the generic penetration rate increased to 86 %, the unbranded generic revenue share increased to 17 %, branded products captured only 71 % of revenues, and branded generics obtained 12 % of total medicine spending.[13]

Stylized Facts Regarding European Small Molecule Generic Market Evolution

Although recent trends in generic efficiency improvements and average price reductions have accelerated, European small molecule generic efficiency rates have not been as high and average molecule prices have not fallen as much proportionately

[10] See Aitken et al. (2008) for details.

[11] Berndt and Aitken (2011); Reiffen and Ward (2007).

[12] IMS Institute for Healthcare Informatics (2011a, p. 21).

[13] IMS Institute for Healthcare Informatics (2014, p. 40).

as has occurred in the U.S. There are several reasons behind this historically less aggressive generic diffusion and pricing in European countries than in the U.S.

First, on-patent brand prices in Europe are generally lower than in the U.S. Even if a manufacturer launching a new drug launches it at parity pricing across the globe, in many European countries there are various forms of price controls, such as prohibitions on manufacturers raising prices more rapidly than some measure of overall national price inflation. This constrains European post-launch on-patent brand price growth, and so when patent expiration occurs, the brand's price relative to its price at time of initial launch is typically lower than in the U.S. This makes generics less of a "bargain" to European payers and consumers. It also implies that entry by generic manufacturers is not as profitable, thereby reducing incentives for, and mitigating the extent of, entry by generic manufacturers.

Second, and related to lower European brand prices than in the U.S., in most European countries the purchasing of medicines is centralized in national or regional governments, providing them with critical monopsonistic leverage in negotiating prices with manufacturers marketing patent-protected medicines. In some countries, such as the U.K. and Germany, in order to gain reimbursement from payers, manufacturers are required to provide data (via a national health technology assessment) showing their drug is at least as if not more cost-effective relative to existing treatments and their outcomes. Relative to this European standard, the U.S. market is much more fragmented, and up to this point in time has not demanded as much comparative cost-effectiveness data.

Third, in the U.S. the possibility of being the exclusive generic entrant for the first 180-days following loss of exclusivity acts as a powerful lure to generic firms, for during that 6 month time frame the successful generic challenger can monopolize substitution away from the off-patent brand, and by pricing just under the brand's umbrella price, the generic can capture a substantial temporary profit bonanza.[14] Comparable "Paragraph IV Challenge" provisions to the U.S. Hatch-Waxman legislation do not exist in most European countries.

Fourth, as has been pointed out convincingly by Danzon and Furukawa (2011), in the U.S. and in only several European markets, dispensing pharmacies face national healthcare reimbursement policies that direct whether brand-generic decision making is driven largely by pharmacies, by incentivizing patients with lower copayments for generic drugs, mandating generic for brand substitution, and inducing pharmacies to aggressively seek out the lowest-cost generic available among the generic manufacturers. By contrast to these pharmacy driven markets, Danzon and Furukawa describe physician-driven markets as ones in which physicians typically prescribe a specific off-patent molecule by brand name or the originator brand name, in which case generic suppliers are incentivized to compete on brand image rather than on price. Although there are differences among them, at the time Danzon and Furukawa (2011) were writing their article, they characterized the U.S., U.K.,

[14] For a discussion of the lucrative profitability of a successful Paragraph IV first to file challenger, even if the brand responds by launching an authorized generic, see, for example, Drug Channels (2011, 2012).

Netherlands and Canadian markets as pharmacy driven and Germany as becoming more so over time, whereas most other European markets (including France, Italy and Spain) were characterized by them as physician driven. Danzon–Furukawa document that pharmacy acquisition costs are generally lower in pharmacy driven markets, other things equal. Their empirical findings are largely corroborated in the eight European country study by Berndt and DuBois (2012).[15]

A related body of literature has examined the effective length of market exclusivity for small molecules across countries. Effective length of market exclusivity has been defined as the time period between regulatory approval of the drug and initial multi-source generic entry (entry may be delayed beyond patent expiration due to the presence of other market exclusivity provisions, such as the 6 month pediatric exclusivity extension in the US). Danzon and Furukawa (2011) report remarkable homogeneity in mean exclusivity length across the nine countries in their sample, close to 12 years. A similar length of time is reported by Hemphill and Sampat (2012) for the U.S., with "evergreening" attempts by brands to extend exclusivity through filing of additional patents offset roughly equally by "prospecting" patent challengers from generic firms. Hemphill and Sampat (2012) report relative stability with a mean of about 12 years for small molecules between 1991 and 2001. Slightly different findings have been reported by Grabowski and Kyle (2007), who suggest that for small molecules in the U.S., effective patent life has declined slightly over the last few decades.

Due to the very small number of biosimilar entries approved to date in the EU and US, there do not appear to be any studies yet comparing effective market exclusivity durations for biologics across countries.

With virtually no biosimilars in the US on which to provide pricing and entry empirical evidence, some insights might be gained by examining studies of specialty drugs as they lose exclusivity in the U.S. because like biologics many of the specialty drugs are injectable or infused and quite costly when under patent protection. To the extent biosimilar entrants will be therapeutic substitutes rather than be rated as fully interchangeable by the FDA,[16] one might plausibly view the amount of entry and the degree of price decrease from entry observed after LOE in specialty drugs in the U.S. as providing an upper bound to the extent of entry and magnitude of price effects likely to occur as biologics go off patent in the U.S.

[15] Berndt and DuBois (2012) amend the Danzon and Furukawa (2011) classification slightly, characterizing France as becoming pharmacy driven in 2006 (when pharmacies were first given strong financial incentives to substitute generics for brands) and Germany in 2007.

[16] According to the FDA (2014b, p. 15), biosimilarity means that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components," and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product." Regarding interchangeability decisions, in the same FDA (2014b, pp. 5–6) document, draft guidance specified four possible process decision outcomes: definitely not interchangeable; might be interchangeable if enough clinical and analytical data to support it is developed; looks like it is interchangeable but needs more clinical and analytical data to support it; and biosimilar is a "fingerprint" of the innovator product, as demonstrated by analytical data, and no further clinical data is required.

The upper bound interpretation is supported by the fact that many generic specialty injectable or infused drugs are essentially small molecules dissolved in water. They do not have the manufacturing complexity issues that arise in creating biologics, although they do have some manufacturing complexity relating to ensuring that they are sterile and may require thermal and/or lighting-constrained distribution and storage.

In this context, it is useful to examine recent research by Conti and Berndt (2014) focusing on 41 cancer molecules (15 oral, 26 physician-administered injectable/infused) that faced initial LOE in the U.S. between 2001 and 2007. A number of the conclusions are particularly relevant. First, entry by generics following the brand's LOE was generally quite modest, and certainly much smaller than that typically observed for small molecule tablets and capsules: the mean number of ANDA sponsors entering a new molecule formulation after LOE ranged from 1.66 in 2003 to 4.9 in 2007, with what appears to be an upwards trend in entry count in 2006 and 2007 compared to previous years. Among several specialty drugs, exit by the branded manufacturer in the first few years following LOE was observed, as well as delayed and sequential ANDA entry into a given molecule undergoing LOE. Among another subset of drugs that were always generic between 2001 and 2007, the average number of manufacturers declined from 3.04 in 2001 to 2.3 in 2007, suggesting that generic manufacturers of cancer drugs may have been exiting from producing very old generic drugs and instead entering into segments experiencing initial LOE that offered potentially more profitable opportunities. Market size as measured by brand revenues for the molecule pre-LOE, the number of distinct indications for which the molecule was FDA approved or reimbursed by Medicare, and oral (as distinct from injected/infused) formulations increased the extent of entry. Although no monoclonal antibodies experienced initial LOE in this 2001–2007 sample time period, the results suggest that to the extent current on-patent monoclonal antibodies are large revenue products (such as Humira™ and Rituxan™), and are used to treat multiple indications, we can expect that as monoclonal antibody agents experience initial LOE in the US in the near future, they will attract a substantial number of biosimilar or biobetter entrants.

In this sample branded prices rise and generic prices fall in response to LOE and generic entry, with the brand price increases being considerably larger for injected/infused than for oral drugs, but decelerating as the number of generic manufacturers increased. While generic prices of oral formulations fall rapidly and steeply as the number of manufacturers increases, for injected/infused drugs generic prices fall more modestly as the number of manufacturers increased.

In terms of total generic plus brand volume following LOE, a common finding among the specialty cancer drugs was that total volume post-LOE was greater than that pre-LOE; this result may be unique to cancer drugs since a common phenomenon in oncology, but not widely observed elsewhere, is that newly approved drugs are combined with old off-patent oncologic agents in cocktail combination treatments. This positive volume impact is also larger for oral than for injected/infused cancer drugs.

Manufacturing Distinctions of Biopharmaceuticals

The manufacturing processes for biologic drugs are considerably more complex and costly than for traditional small molecules that are formulated as oral tablets/capsules. Classic small molecules pharmaceuticals such as aspirin are chemically synthesized and manufactured into tablets or capsules to be taken orally by patients. Biopharmaceuticals, or biologics, such as insulin and monoclonal antibodies, are large molecules usually produced by unicellar organisms (such as yeast or microbes) or by immortalized mammalian cells in large fermentation vessels. The large molecules are then purified from the cellular broth and formulated for administration to patients by injection or infusion to avoid their gastro-intestinal tract which would digest these biologic products. Because of their scientific and manufacturing differences, small molecule and biologic pharmaceuticals are subject to somewhat different regulatory rules and clinical handling which in turn may affect their development, distribution, reimbursement, competition, product life cycles and so economic incentives. Prior research suggests that the commercial experiences of biologics and small molecules differs significantly.[17]

Due to their size and propensity to fold into different conformations, biologics can be difficult to chemically characterize fully, as is typically done with small molecule pharmaceuticals. A famous set of rules for successful small molecule properties was developed by a Pfizer chemist and his colleagues after examining many successful, and failed, candidate drugs.[18] Now called the Lipinski rule of five, some of the rules state that successful drugs have a molecular weight less than 500, the number of hydrogen donating groups is less than five, and the total number of hydrogen atoms should be less than ten. Biologics violate all these rules. For example, the molecular weights of somatropin, erythropoietin alpha and filgrastim are 22,124, 30,400 and 18,800 respectively. Each is a folded protein consisting of a chain of amino acids. Depending on the product, the chain ranges from 165 to 191 amino acids long. Hence, since any single amino acid has at least two oxygen atoms and a nitrogen atom, each of these biologics clearly violates most of Lipinski's rules for a successful pharmaceutical.

Due to their size and complexity, fully characterizing a biologic through physiochemical means such as is used for pharmaceuticals or biological assays is not currently possible. Furthermore, the links among such features and medically important characteristics such as bioequivalence, interchangeability among products, immunogenicity, pharmacokinetics/dynamics, metabolism and even safety and efficacy are not yet well understood.[19]

The molecular size of biologics raises manufacturing and quality control issues that also confront biosimilar manufacturers. Biomanufacturing is complex, requiring isolation of the DNA or RNA to produce the protein, insertion of that DNA/RNA

[17] Trusheim et al. (2010).

[18] Leeson (2012).

[19] Schellekens (2005).

into a cell line and optimization of it for production, establishment of fermentation conditions, development of purification processes and the logistics of packaging, distribution and storage to preserve the protein. The result is that biopharmaceutical production costs are relatively high with cost of goods sold ranging from 15 to 30 % for today's products,[20] significantly higher than that for small molecule pharmaceuticals. It is unclear if biosimilars will achieve lower production costs or experience higher costs than the reference product(s). Some estimate that biosimilar manufacturers will be unable to exploit the economies of scale or match the accumulated expertise of established players, and so may incur substantially higher unit costs.[21] However, new bioproduction technologies may enable substantially lower unit production costs through lower capital costs and with higher product yields through modern cell lines, but whether they will still be designated as fully interchangeable products with the brand by regulators is uncertain.[22]

Given this regulatory uncertainty (on which, more below) and potentially greater average production costs, it may be more attractive economically for biologic manufacturers to pursue a "biobetter" product entry strategy with an NDA/BLA rather than an abbreviated biosimilar application, consciously differentiating their product from the brand that is now off-patent, rather than seeking biosimilar approval, even though with the latter the number of clinical investigations and costs are likely to be smaller. Other factors affecting the choice between a biosimilar or biobetter strategy include the ease and speed of patient recruitment, the speed with which manufacturing facilities are approved, the willingness of prescribers and payers to adopt biosimilars, concerns regarding immunogenicity, regulatory restrictions on marketing claims, and legal liability. Many of these factors are likely to vary across geographies. Hence with regulatory, commercial and scientific uncertainty all playing critical roles, it is plausible that the choice between biosimilar and biobetter strategies will differ in the US and EU, and depend on more than simply the degree to which EMA-FDA regulatory policies are harmonized or divergent.

With this as background, we now examine the accumulating evidence on biosimilar uptake trends in Europe since 2006.

European Evidence on Biosimilar Uptake

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued draft guidelines on similar biological medicinal products in November 2004, which were adopted by CHMP in September 2005 and came into effect on 30 October 2005.[23] According to the guidelines, products will be evaluated on a case-by-case basis but the general approval pathway will be abbre-

[20] Ziegler and Santagostino (2011).

[21] Kelley (2009).

[22] Morrow (2006).

[23] European Medicines Agency (2005).

viated relative to an entirely new biologics product application. This framework includes an overarching set of principles; general guidelines on quality, safety and efficacy; and guidelines specific to product classes. To date, the EMA has issued class-specific guidelines in seven classes,[24] and guidance is under development for several other major biologics product classes including recombinant follicle stimulation hormone, and recombinant interferon beta.[25] The EMA has also approved biosimilars in five product classes—somatropins, erythropoietins, granulocyte colony-stimulating factors (G-CSFs), tumor necrosis factor alpha (TNF-α, infliximab), and human follicle stimulating hormone (FSH, follitropin α).[26] An appendix to this paper provides further details on the reference products, biosimilars, and non-reference products in these five product classes.

Table 1 lists the EMA action history on biosimilars from the inception of the program up to April 18, 2014. Applications currently under review and those which were submitted and then withdrawn prior to EMA action (such as the Marvel applications for insulin biosimilars) are not included.

Sandoz's Omnitrope human growth hormone product was the first biosimilar approved in the EU (April 12, 2006) with Pfizer's Genotropin serving as the reference product.[27] As of June 2010, 14 biosimilars for somatropin, epoietin and filgrastim/lenograstim had been approved and were being marketed in the EU: seven for filgrastim (a granulocyte colony stimulating factor), two for somatropin (growth hormone), and five for short-acting epoietin.

The mid-2010 to 2013 lull having only limited EMA approval action activity was broken in the autumn of 2013 with CHMP recommendations for an eighth filgrastim biosimilar, for the first two biosimilars for a monoclonal antibody and for a fertility hormone. Remsima and Inflectra are both biosimilars for infliximab using Janssen's Remicade as the reference product. Monoclonal antibodies are perhaps the largest class of biologic products, both in terms of numbers of products as well as global revenues. From 2006 through mid-2010 the EMA had ruled on 15 biosimilar applications, approving all but one.

In the middle period (2010–2013) the EMA subsequently withdrew approval for two of the products and approved none. In addition it saw Marvel LifeSciences withdraw its applications for three insulin biosimilars.[28] The EMA noted that the company had stated that, "the decision to withdraw is in order to have sufficient time to repeat and submit bioequivalence T1D (type 1 diabetes) PK/PD

[24] The product-specific biosimilar guidelines include recombinant erythropoietins, low-molecular-weight heparins, recombinant interferon alpha, recombinant granulocyte-colony stimulating factor, somatropin, recombinant human insulin, and monoclonal antibodies. See European Medicines Agency (2006a, b, c, 2009a, b, 2010, 2012a, b, c).

[25] European Medicines Agency (2010, 2011a, b, c, 2012a, c (a finalized version of 2010))

[26] European Medicines Agency (2013a).

[27] European Medicines Agency (2013a, p. 4). BioPartners' Valtropin was approved by the EU on the same day as Sandoz' Omnitrope with Humatrope as the reference product, but Valtropin has not been marketed.

[28] European Medicines Agency (2012b).

Table 1 European biosimilar regulatory reviews and current marketing status[a]

EMA biosimilar rulings						
Trade name	Active substance	Biosimilar sponsor	Reference product	Therapeutic area	Decision	Date
Omnitriop	Somatropin	Sandoz	Genotropin	Tumer Syndrome, Pituitary Dwarfism, Prader-Willi Syndrome	Approve	April 12, 2006
Valtropin	Somatropin	BioPartners	Humatrope	Tumer Syndrome, Pituitary Dwarfism	Approve	April 24, 2006
					Withdrawn	May 20, 2012
Alpheon	Interferon alpha-2a	BioPartners	Roferon-a		Reject	June 28, 2006
Abseamed	Epoetin alpha	Medice	Eprex	Chronic Kidney Failure, Anemia, Cancer	Approve	August 28, 2007
Binocrit	Epoetin alpha	Sandoz	Eprex	Chronic Kidney Failure, Anemia	Approve	August 28, 2007
Epoetin alfa Hexal	Epoetin alpha	Hexal	Eprex	Chronic Kidney Failure, Anemia, Cancer	Approve	August 28, 2007
Retracrit	Epoetin zeta	Hospira	Eprex	Anemia, Autologous Blood Transfusion, Cancer, Chronic Kidney Failure	Approve	December 18, 2007
Silapo	Epoetin zeta	STADA	Eprex	Anemia, Autologous Blood Transfusion, Cancer, Chronic Kidney Failure	Approve	December 18, 2007
Biograstim	Filgrastim	CT Arzneimitel	Neupogen	Cancer, Hematropoietic Stem Cell Transplantation, Neutropenia	Approve	September 15, 2008
Filgrastim ratiopharm	Filgrastim	Ratiopharm	Neupogen	Cancer, Hematropoietic Stem Cell Transplantation, Neutropenia	Approve	September 15, 2008
					Withdrawn	July 20, 2011
Ratiograstim	Filgrastim	Ratiopharm	Neupogen	Cancer, Hematropoietic Stem Cell Transplantation, Neutropenia	Approve	September 15, 2008
Tevagrastim	Filgrastim	Teva	Neupogen	Cancer, Hematropoietic Stem Cell Transplantation, Neutropenia	Approve	September 15, 2008
FilgrastimHexal	Filgrastim	Hexal	Neupogen	Cancer, Hematropoietic Stem Cell Transplantation, Neutropenia	Approve	February 6, 2009

(continued)

Table 1 (continued)

EMA biosimilar rulings						
Trade name	Active substance	Biosimilar sponsor	Reference product	Therapeutic area	Decision	Date
FilgrastimZarzio	Filgrastim	Sandoz	Neupogen	Cancer, Hematropoietic Stem Cell Transplantation, Neutropenia	Approve	February 6, 2009
Nivestim	Filgrastim	Hospira	Neupogen	Cancer, Hematropoietic Stem Cell Transplantation, Neutropenia	Approve	June 8, 2010
Remsima	Infliximab	Celltrion	Remicade	Rheumatoid Arthritis, Crohn's Disease, Ulcerative Colitis, Ankylosing Spondylitis, Psoriatic Arthritis and Psoriasis	Approve with monitoring	September 9, 2013
Inflectra	Infliximab	Hospira	Remicade	Rheumatoid Arthritis, Crohn's Disease, Ulcerative Colitis, Ankylosing Spondylitis, Psoriatic Arthritis and Psoriasis	Approve with monitoring	September 9, 2013
Ovaleap	Follitropinalfa	Teva	Gonal-f	Anovulation	Approve with monitoring	September 27, 2013
Grastofil	Filgrastim	Apotex Europe	Neupogen	Neutropenia	Approve with monitoring	October 18, 2013

[a]European Medicines Agency (2013a, b, 2014)

(pharmacokinetic/pharmacodynamic) data on each clamp study in order to comply with the planned new insulin guideline…, at a validated CRO (contract research organization)."[29] This experience demonstrated the impact that regulatory guidance regarding the level of evidence required from sponsors to demonstrate biosimilarity can have on the number and timing of biosimilars. Compared to small molecule generics, the amount of scientific and clinical effort required for biosimilar determination by regulatory authorities such as the EMA is significantly greater.

Instead of documenting efficacy and safety of the follow-on biologic via clinical trials, for therapeutic substitutability a follow-on biologic must prove biosimilarity. To date the EMA has required at least one Phase II or Phase III clinical trial for a biosimilar to demonstrate similar safety and efficacy to its reference molecule. Notably, the EMA framework does not result in any findings of interchangeability, with questions of substitutability being left to the member state competence to regulate. Local substitution laws differ among EU member states, with some (e.g., Spain, Sweden) including explicit prohibition on automatic substitution for biologics (i.e., prohibiting mandatory pharmacy-level substitution).[30] This contrasts with US policy, by which the FDA approves applications as therapeutic substitutes or interchangeable therapies. Within the EU framework, the EMA also determines the extent to which biosimilarity of a biologic for treatment of one indication can be extrapolated to other indications for which the reference biologic had received EMA approval.[31]

Of note in the US, there has been considerable activity at the state legislature level, with legislation being introduced frequently following the principles advocated for by organizations such as the Biotechnology Industry Organization (BIO). Specifically, the principles BIO advocates that states should follow include: (1) substitution should occur only when the FDA has designated a biologic product as interchangeable; (2) the prescribing physician should be able to prevent substitution; (3) the prescribing physician should be notified of the substitution; (4) the patient, or the patient's authorized representative, should, at a minimum, be notified of the substitution; and (5) the pharmacist and the physician should keep records of the substitution.[32] Other countries have used a European-like approach, including Canada (where biosimilars are termed "subsequent entry biologics", or "SEBs") and Japan. Australia adopted the EU guidelines in August 2008.[33]

Because the phenomenon of biologic patent expiration is only a relatively recent development, the evidence on pricing of biologics to date is rather sparse. One publicly available peer-reviewed article is that by Calfee and DuPre (2006), who find that while the first generation of biologics (such as the "branded generic" insulins) were priced substantially lower in Europe than in the U.S., the later generation

[29] European Medicines Agency (2012b).

[30] Ehmann (2010).

[31] European Commission (2013, p. 27).

[32] Biotechnology Industry Association (2013). For additional discussion, see Karst (2013a), who also provides a state-by-state legislation scorecard.

[33] Grabowski et al. (2013, p. 3).

single source branded biologics were priced close to parity in Europe and the U.S. Whether prices of more recent cohorts of newly launched branded biologics are parity priced in Europe and the US is unknown.

However, a recent publication, by Grabowski et al. (2011, updated in 2013, p. 24) surveys various U.S. studies that have projected biosimilar price discounts relative to pre-entry U.S. brand prices. Grabowski et al. (2007a, b) projected a 10–30 % discount in year 1, the Congressional Budget Office (2008) a 20 % discount in year 1 increasing to 40 % by year 4, Steve Miller and Jonah Houts (2007) of Express Scripts 25 % in year 1, and Roland (Guy) King (2007) of Avalere Health a 20 % discount in year 1 increasing to 51 % in year 3. Notably, each of these projected discounts for biosimilars is considerably less than the discounts achieved in recent years by generic small molecules in the U.S.,[34] but is in the range of injected/infused cancer specialty drugs experiencing initial LOE in the U.S. in 2001–2007.[35]

Before presenting empirical evidence from biosimilars in the EU, we digress briefly to focus on some measurement issues. Because some medicines are used to treat diverse conditions having very different dosages across individuals (such as those based on weight or body mass index) and indications, measuring the volume of these multipurpose medicines is very challenging. The IMS Health Midas sales data in local currencies and extended units that we employ are derived from ex-manufacturer invoices; these data therefore reflect revenues received by manufacturers, they exclude wholesale and retail margins, and therefore do not reflect actual reimbursements by national health authorities or other payers to the retail sector. The local currency sales have been converted to US dollars at contemporaneous quarterly varying exchange rates, for all countries.

Some researchers transform these data into days of therapy utilizing the World Health Organization (WHO) Defined Daily Dosage (DDD) metric. The WHO Collaborating Center for Drug Statistics and Methodology defines the DDD as follows:

> "The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults…. It should be emphasized that the defined daily dose is a unit of measurement and does not necessarily reflect the recommended or Prescribed Daily Dose. Doses for individual patients and patient groups will often differ from the DDD and will necessarily have to be based on individual characteristics (e.g. age and weight) and pharmacokinetic considerations…. Drug consumption data presented in DDDs only give a rough estimate of consumption and not an exact picture of actual use. The DDD provide a fixed unit of measurement independent of price and dosage form (e.g., tablet strength) enabling the researcher to assess trends in drug consumption and to perform comparisons between population groups…. *The DDD is nearly always a* ***compromise*** *based on a review of the available information including doses used in various countries when the information is available. The DDD is sometimes a dose that is rarely if ever prescribed, because it is an average of two or more commonly used doses*."[36]

[34] Aitken et al. (2008), Berndt and Aitken (2011) and Aitken et al. (2013).

[35] Conti and Berndt (2014).

[36] World Health Organization (2009, pp. 1–2); italics and bold in original text. For further details concerning DDD, see World Health Organization (2003 (Chap. 6), 2011); also see International Federation of Pharmaceutical Manufacturers and Associations (2006).

For our purposes, it is useful to note that the WHO DDD assigned to a drug is time invariant, and is identical across countries and dosage strengths. While it would be preferable to utilize the IMS Health daily average consumption (DACON) metric derived and updated from actual retail prescription data, as in Berndt and Aitken (2011), currently IMS Health DACON data are only available for some countries, and they are often not available for medicines dispensed outside the retail sector (thereby excluding biologics administered in hospitals or outpatient clinics).

Other possible volume measures include extended units, standard units, and eaches. *Extended units* are the number of tablets, capsules, milliliters, ounces, etc. of a product shipped in each unit. This number is calculated by multiplying the number of units by the product size. According to IMS, "…extended units are not meaningful above the package level, because a product may have different forms and strengths and therefore a different type of unit for each presentation."[37] *Standard units* represent the number of dose units sold for a particular product. Examples of standard units are the number of tablets sold, the number of 5-ml doses for liquid products sold, or the number of vials sold. According to IMS personnel, "Standard units enable you to compare sales volume data for products across different product forms and dosing regimens. For example, you can compare solid to liquid forms more precisely by equating the number of milliliters of a liquid preparation—such as 5 ml of liquid—to the standard solid dosage of one tablet. Standard units are defined for all product forms, allowing you to make accurate comparisons among several product forms."[38] It is our understanding that standard units replaced earlier measures based in part on eaches, and that standard unit measures for MIDAS and other IMS data bases such as the U.S. National Sales Perspective are not available before 2006. Regarding *eaches*, IMS personnel indicate that eaches represent "the number of single items (such as vials, syringes, bottles, or packet of pills) contained in a unit or shipping package and purchased by providers and pharmacies in a specific time period. An each is not a single pill or dosage of medicine (unless one package consists of a single dose). An each may be the same as a unit if the unit does not subdivide into packages. Eaches are usually used to look at injectable products. Eaches are most meaningful at the package level, since packages and their subunits may contain different quantities of strengths and volumes."[39]

As we shall see when discussing biosimilar utilization studies appearing in the existing literature, various researchers have differed in their choice of volume measure. DDD requires assumptions about actual clinical use, whereas standard units is more directly observable. Thus for gross market analyses, standard units may be a preferable measure to DDD. However, it is our understanding that standard units do not always account properly for unit size differences (e.g., a vial is a vial regardless of ml volume). In the results of our utilization research presented later in this section, we employ standard units; by contrast, Grabowski et al. (2011, 2013) employ DDDs

[37] From email correspondence with Terry McMonagle at the IMS Institute for Healthcare Informatics, September 4, 2013, 11:15 am.

[38] See footnote 37.

[39] See footnote 37.

as their unit of volume measure, while in Grabowski (2013) volume measures are entirely omitted and only dollar revenue share data are presented.

One other issue meriting discussion is that considerable diversity exists across molecules and countries in the setting in which biologics are dispensed such as retail pharmacies, physicians' offices or hospitals.[40] Not only might this affect which volume measure is most appropriate for a particular molecule, but because of the extensive tendering that occurs for hospitals in Europe, actual and average measured prices of biologic molecules could depend on the composition of dispensing sites. As best we understand it, to the extent the tendering process results in rebates paid by manufacturers to national or regional health authorities, these rebates are unlikely to be reflected in the invoice prices monitored by the IMS MIDAS data system.

We begin our overview of biosimilar diffusion in certain EU countries by discussing the Grabowski et al. (2013) results that utilized 2007–2009 DDD data for five large EU countries, and then update and compare our new analyses using more recent IMS Health MIDAS standard unit measures and a larger number of countries.

Table 2 above summarizes biosimilar DDD volume shares in five large European countries—France, Germany, Italy, Spain and the U.K.—for three molecules—somatropin, erythropoietin alpha, and granulocyte colony stimulating factor (G-CSF) from 2007 to 2009, as reported in Grabowski et al. (2013, Table 2, p. 6). The most striking finding is the absence of any pattern—the extent of biosimilar penetration varies substantially both across therapies within a country, and across countries for the same therapy. Through 2009, Germany exhibited the highest level of aggregate demand and market share for any biosimilar product (a 62 % market share for erythropoietin alpha in 2007). According to one analyst, Germany's influential Federal Healthcare Committee which has jurisdiction over which products and services are reimbursed, has in fact embraced biosimilars wholeheartedly, and reinforced its preference by implementing a reference pricing system. Germany also has placed specific targets or quotas for physicians and sickness funds for biosimilars that vary geographically. Finally, Germany has become the dominant source of biosimilar manufacturing in Europe.[41]

Relative to that in Germany, the uptake of biosimilars in other European countries through 2009 was much slower. Recall that while EMA approval is necessary for a biosimilar to be marketed in EU member countries, actual sales may be delayed since reimbursement must still be negotiated between manufacturers and regional/national government payers. This reimbursement approval delay may be partly responsible for later biosimilar entry dates in several European countries.

For erythropoietin alpha, in Germany the biosimilar products accounted for 62 % of total biosimilar and innovator erythropoietin products sold in 2009, within 2 years of its launch. However, the cross-country heterogeneity in biosimilar takeup is sub-

[40] See Walsh (2013) for examples and discussion.

[41] The analyst's comments are referenced in the note below Table 2 of this document; also see Walsh (2013).

Table 2 Initial biosimilar competition in selected EU countries: market share evidence biosimilar unit share of the molecular entity, 2007–2009

	France (%)	Germany (%)	Italy (%)	Spain (%)	U.K. (%)
Somatropin					
2007	2	3	6	1	0
2008	10	6	17	1	0
2009	16	8	27	5	1
Erythropoietin alpha					
2007	0	0	0	0	0
2008	0	35	0	0	0
2009	4	62	0	4	1
Granulocyte colony stimulating factor					
2007	–	–	–	–	–
2008	0	1	0	0	2
2009	7	17	N/A	9	21

Notes: Taken from Grabowski et al. (2013, p. 6). An endnote adds that "Data are based on IMS Midas data as reported in Rovira et al. (2011). Biosimilar share of unit sales are measured based on Defined Daily Dose. Biosimilar G-CSF was not launched until 2008, so biosimilar shares for 2007 are not reported in Table 3. For G-CSF in Italy in 2009 the biosimilar share is recorded as N/A to reflect insufficient data for calculating a biosimilar share—fewer than 5,000 DDDs were reported in the data for combined innovator and biosimilar unit sales in Italy that year."

stantial; for France and Spain the erythropoietin biosimilar share was only 4 %, and even less at 1 and 0 % for the U.K. and Italy, respectively.

Cross-country patterns are quite different for G-CSF (filgrastim). As seen in Table 2 above, biosimilar shares for G-CSF in 2009 ranged from 7 % in France to 21 % in the U.K., with Spain at 9 % and Germany at 17 % being in between. Biosimilar sales of G-CSF in 2009 failed to reach minimum reporting thresholds in Italy.

Finally, cross-country patterns for biosimilar somatropin differ from those both for erythropoietin alpha and G-CSF. As seen in the top panel of Table 2, in 2009 biosimilar somatropin volume shares were on average larger than for the other biosimilar molecules, with Italy at 27 % having the largest share, followed by France at 16 %, Germany 8 %, Spain 5 % and the U.K. 1 %.

European Relative Biosimilar Volume Shares, 2007–2012

To shed light on the importance of measurement issues concerning whether one measures volume based on DDD vs. standard units, in Table 3 we present standard unit based volume shares for the same five countries for years 2007–2012 as in Grabowski et al. (2013); note that the years 2007–2009 overlap in both Tables 2 and 3, facilitating a direct comparison. We also expand the set of countries to include several smaller ones in northern Europe and Scandinavia: Belgium, Finland,

Table 3 Biosimilar standard unit share of the molecular entity

	France (%)	Germany (%)	Italy (%)	Spain (%)	UK (%)	Belgium (%)	Finland (%)	Norway (%)	Sweden (%)
Somatropin									
2007	1	1	1	0	0	0	0	0	0
2008	5	2	2	0	0	0	0	0	0
2009	7	2	3	1	0	5	0	0	3
2010	9	3	4	1	1	6	0	0	7
2011	10	4	4	2	1	7	5	0	7
2012	11	5	4	3	1	7	5	0	8
Erythropoietin alpha and zeta									
2007	0	2	0	0	0	0	0	0	0
2008	0	41	0	0	0	0	0	0	1
2009	4	58	0	3	3	0	0	0	19
2010	9	64	5	19	7	0	100	0	49
2011	11	69	13	31	10	0	100	100	62
2012	16	68	21	39	7	0	100	100	70
G-CSF (fHgrastim)									
2007	0	0	0	0	0	0	0	0	0
2008	0	0	0	0	1	0	0	0	0
2009	6	8	1	9	20	0	0	25	5
2010	26	15	9	23	53	0	15	0	40
2011	35	23	36	33	71	0	33	0	70
2012	48	27	60	51	81	0	65	20	86

Norway and Sweden. We begin with a comparison limiting our attention to the five large EU countries, and then consider whether the smaller northern European and Scandinavian countries exhibit similar or divergent trends.

For the five large EU countries considered by Grabowski et al. (2013), a comparison of molecular shares for the 2007–2009 overlapping years in Tables 2 and 3 suggests a pattern in which biosimilar shares based on standard units tend generally to be somewhat smaller—in some cases considerably smaller—than those based on DDDs. For example, in 2009 for France, Germany, Italy, Spain and the U.K. the standard unit (DDD) shares for biosimilar somatropin are, respectively, 7 (16 %), 2 (8 %), 3 (27 %), 1 (5 %), and 0 % (1 %); for erythropoietin alpha and zeta the respective molecular shares in 2009 are 4 (4 %), 58 (62 %), 0 (0 %), 3 (4 %) and 3 % (1 %), while forfilgrastim(G-CSF) they are 6 (7 %), 8 (17 %), 1 (N/A), 9% (9 %), and 20 % (21 %).

Looking at years beyond 2009 for the five large EU countries in the first five columns of Table 3, we observe that each of the three products continued to follow a distinct adoption pattern. Across product classes, the most successful of these three biosimilar product classes is filgrastim (G-CSF), the least successful is somatropin, with erythropoietin alpha and zeta being in between. Filgrastim reaches 50 % market share or higher in most large EU countries by 2012 while somatropin

exceeds 10 % share in only one (France) with erythropoietin achieving the most varied market shares, ranging from 7 % in the UK and 16 % in France to 39 % in Spain and 68 % in Germany, the highest single large EU country market share observed.

As with the DDD data, the standard unit data shows that adoption in the first years (2007–2009) was cautious across all five large EU countries and three products, with the exception of erythropoietin in Germany which achieved 50 % market share in only its third year, 2009. In addition to clinicians taking a cautious view to using biosimilars, this slow diffusion may reflect the range of dates for biosimilar regulatory and reimbursement decisions for the products among these five large EU countries.

By 2012, among these five large EU countries, biosimilar filgrastim has become the most widely successful biosimilar product to date, at least as measured in terms of standard unit market shares.[42] Perhaps surprisingly given its rapid initial use of the first biosimilar erythropoietin alpha, Germany has the lowest filgrastim biosimilar market share at 27 %. By 2012, the biosimilar filgrastim share in the U.K. has grown to an impressive 81 %, in Italy it increased from 36 % in 2011 to 60 % in 2012, and in both France and Spain it captured about half the filgrastim product market (48 and 51 % respectively)..

Biosimilar somatropin has continued its gradual but low penetration over time among these five large EU countries, with the greatest penetration being but 11 % for France in 2012, and with all other countries experiencing single digit market shares, usually below 5 %. Of the three products, somatropin is the only one in which France leads the five country usage.

Biosimilars to erythropoietin alpha (including the zeta forms that also used Eprex as a reference product, see Table 1) have maintained and leveled off their market share in Germany at 64–69 %, but the most rapid growth of this biosimilar molecule among the five largest EU countries has occurred in Spain (from 3 to 39 % between 2009 and 2012) and in Italy (from 0 to 21 % between 2009 and 2012). France has seen a steady increase in the biosimilar erythropoietin alpha share, but at 16 % in 2012 this share is still quite low. Finally, in the U.K. the biosimilar erythropoietin alpha share has an uneven trend, increasing from 3 to 10 % between 2009 and 2011, but then falling to 7 % in 2012.

Another common theme from Tables 2 and 3 is that there is significant heterogeneity across the largest EU countries in the penetration of a given biosimilar product, and across products in penetration by country. For example, at 81 % the U.K. has the greatest penetration of biosimilar filgrastim, Germany has the largest penetration of biosimilar erythropoietin alpha at 68 %, and France the highest penetration of biosimilar somatropin at 11 %. Heterogeneity in biosimilar uptake is the dominant theme.

[42] We note in passing that the 81 % biosimilar share reported for filgrastim in the UK in 2012 in Table 3 based on standard unit measures is very similar to the part-year 2013 83 % share for filgrastim in the UK reported in Walsh (2013, slide 8).

Germany adopted biosimilar erythropoietin alpha quickly and has achieved nearly double the relative usage in 2012 with 68 % biosimilar compared to the second place country Spain at 39 % and more than four times the 16 % standard unit market share in France. For somatropin, however, Germany's market share quickly fell behind that of France and in 2012 somatropin biosimilars had only achieved 5 % market share in Germany, half that in France. Moreover, with filgrastim, Germany has achieved the lowest biosimilar penetration of the five countries with only 27 % market share, merely about half of most other countries and only a third that of the leading country, U.K. with 81 %. Biosimilar filgrastim is also strong in Italy where its 60 % biosimilar penetration places second, the country's highest relative rank. Notably, these diffusion rates do not support earlier observations by Senior (2009), and Grabowski (2013) and Grabowski et al. (2011, 2013) based on data ending in 2009, suggesting a German exceptionalism due to its centralized and biosimilar encouraging Federal Healthcare Committee, its biosimilar reference pricing system, specific targets or quotas for physician and sickness funds for biosimilars, and its role as the main source of biosimilar manufacturing in Europe. Moreover, in 2012, Germany lagged in biosimilar use in two of the three product areas, with the U.K. and France leading in the other two.

Perhaps most surprisingly, Spain and Italy which have arguably suffered the most from the austerity of the Great Recession, do not lead in biosimilar use in any of the three products (see Table 3). This lower use of biosimilars in the most cost constrained countries may be changing, however. From 2010 to 2012, Italy's use of biosimilar filgrastim lept from last place at 9 % biosimilar penetration to a second place 60 % penetration in 2012. Similarly, Italy's acceptance of biosimilar erythropoietin moved from essentially none to 12 %, surpassing the penetration achieved in France and the U.K. We conclude, therefore, that among the five largest EU countries, the adoption of biosimilars remains dynamic with a stable equilibrium between biosimilar and branded drugs apparently not yet achieved.

It may be instructive, however, to expand the analysis to examining biosimilar uptake trends in smaller EU countries, such as Belgium and the Scandinavian countries of Finland, Norway, and Sweden; biosimilar uptake shares for these four countries are presented in the final four columns of Table 3. Perhaps the most striking result is that while Belgium has been very slow in converting to biosimilars, the Scandivanian countries initially delayed in biosimilar uptake, but since 2010 their penetration of biosimilars has been dramatically rapid and deep. For somatropin (the top panel in Table 3), biosimilar penetration has been modest—greater than that of France but less than that of the four other large EU countries. For erythropoietin alpha and zeta, however, by 2011 both Finland and Norway achieved 100 % biosimilar penetration, with Sweden in 2012 at 70 % being even more biosimilar-friendly than Germany at 68 %. In the case of filgrastim, while Norway at 20 % biosimilar volume share is lower than that of any of the large five EU countries, at 65 % Finland is second only to the U.K. among the large five EU countries, and Sweden tops them all with an 86 % biosimilar standard unit volume market share. In stark contrast to the Scandinavian countries, Belgium's adoption of biosimilars is strikingly small—only 7 % of somatropin in 2012, and no biosimilar adoption through 2012 for both erythropoietin alpha and zeta and filgrastim. It should be

noted that volumes in these countries tend to be quite low and therefore substantial share changes may be driven by alterations in but a few contracts or by a few medical groups.

In summary, Germany experienced a rapid uptake of biosimilars, but the adoption rate has stabilized since about 2009. Scandinavian countries delayed their initial adoption, but their acceptance of biologics has been very rapid and deep since then. Belgium's transition to biosimilars has been among the slowest and shallowest among the nine EU countries examined here.

European Relative Biosimilar Revenue Shares, 2007–2012

It would normally be plausible to expect that the revenue weighted shares of biosimilars will be much lower than standard unit market shares, since it is usually assumed that biosimilars will be priced significantly lower than the reference product and other branded, first to market products in the same class. Table 4 shows the revenue market shares of biosimilars in the same format used for standard unit market shares in Table 3, not only for the three products in the five largest EU countries studied over the 2007–2009 time period by Grabowski et al. (2013), but also updated for 2010–2012 and expanded to four other northern European and Scandinavian countries. Again the analysis is based on aggregated quarterly IMS MIDAS data in which revenues were collected in local currencies and converted to US Dollars using the exchange rate in effect for that period. Data for the five large EU countries considered by Grabowski, Long and Mortimer are presented in the first five columns of Table 4, while that for the additional four countries we examine are in the final four columns.

Like the standard unit market shares in Table 3, even within the five largest EU countries the dollar shares in Table 4 exhibit a wide range of values among products and countries. However, some of the relative positions of the countries change. For instance, Germany biosimilar filgrastim use in 2012 came in lowest at 27 % among the five largest EU countries when using standard unit measures (Table 3) but biosimilar filgrastim's share doubles to 54 % in Germany when using dollar share (Table 4), placing it in a tie for second with Italy, but still trailing the UK's 81 % share. For somatropin, Spain's second to last place in standard units (3 %) rises to a 10 % share using dollar revenue share placing it in first place before France whose dollar share at 9 % is slightly lower than the 11 % standard unit share. The relative country rankings among the five largest EU countries for erythropoietin alpha/zeta remain unchanged.

Turning to standard unit (Table 3) vs. dollar (Table 4) shares for the three biosimilar molecules in the four additional countries (Belgium, Finland, Norway and Sweden), for somatropin we observe Belgium's dollar shares are slightly smaller than its standard unit shares (although both are small), but for Finland and Sweden the dollar shares are larger than the standard unit shares. Across all nine countries, Norway has the smallest and France the largest somatropin standard unit shares, and while Norway continues to have the smallest somatropin biosimilar dollar

Table 4 Biosimilar dollar share of the molecular entity

	France (%)	Germany (%)	Italy (%)	Spain (%)	UK (%)	Belgium (%)	Finland (%)	Norway (%)	Sweden (%)
Somatropin									
2007	1	1	1	0	0	0	0	0	0
2008	3	2	2	1	0	0	1	0	0
2009	5	2	4	2	1	3	3	0	4
2010	7	4	5	5	1	3	4	0	11
2011	8	5	6	7	1	4	5	0	11
2012	9	6	5	10	2	5	6	0	14
Erythropoietin alpha and zeta									
2007	0	1	0	0	0	0	0	0	0
2008	0	32	0	0	0	0	16	1	2
2009	3	50	0	2	4	0	55	3	21
2010	10	60	4	9	7	0	84	3	52
2011	12	69	9	15	9	0	97	54	65
2012	19	72	17	26	8	0	99	66	73
G-CSF (*fHgrastim*)									
2007	0	0	0	0	0	0	0	0	0
2008	0	0	0	0	1	0	0	0	0
2009	5	22	1	7	19	0	0	12	5
2010	20	35	7	17	54	0	11	5	29
2011	28	47	30	24	73	0	29	4	57
2012	43	54	54	48	81	1	54	9	80

shares (at zero), Sweden's dollar shares for somatropin biosimilars is larger than any of the other eight EU countries. Notice also that in Finland and Sweden, the switch from branded to biosimilar occasionally happens completely within a single year, e.g., Finland in 2010 and Norway in 2011 for erythropoietin alpha and zeta. A plausible hypothesis is that the volumes in these countries are quite small, so that simply switching a small number of contracts (perhaps just one?) results in dramatic product share changes.

Whether measured in terms of standard unit or dollar shares, diffusion of biosimilar versions of erythropoietin alpha and zeta, as well as filgrastim, in to Belgium is virtually nil. In sharp contrast, while the diffusion of biosimilar erythropoietin alpha and zeta among the five large EU countries was most rapid and deep for Germany (whether measured in shares of standard units or dollars), in both Norway and Sweden the extent of diffusion of this biosimilar molecule is close to that of Germany, and in the case of Finland the biosimilar share of erythropoietin alpha and zeta approaches 100 %.[43] Relatively slow and shallow adoption of biosimilar fil-

[43] The dollar and standard unit shares do not show complete concordance for Finland and Norway. The underlying IMS MIDAS data shows some minimal reference product dollar sales in spite of zero standard unit shipments. This could be due to reporting timing differences or other idiosyncratic causes affecting the very small values.

grastimis observed in Belgium and Norway, but as with erythropoietin alpha and zeta, adoption of biosimilar filgrastim by 2012 is very substantial in both Finland and Sweden. Although the relative standard unit/dollar share sizes differ among the four small EU countries for somatropin (standard unit shares larger than dollar shares for Belgium, smaller for Finland and Sweden, both zero for Norway), for erythropoietin alpha and zeta by 2012 standard unit (dollar) shares for Finland and Norway are at 100 % (99 and 66 %, respectively), for Sweden in all years the dollar shares of this biosimilar molecule are slightly greater than the standard unit shares. Finally, the same country patterns of share inequalities holds in the case of filgrastim: standard unit shares are greater than dollar shares for Finland and Norway, but the reverse inequality is observed in Sweden.

It is not clear what accounts for the differences between the standard unit and dollar shares. As reported above, while in most cases dollar shares are larger than shares in standard units, this is not always the case (e.g., somatropin in France, epoieten alpha and zeta in Spain, and filgrastim in Italy, Spain, Finland, Norway and Sweden). As discussed earlier, standard units may not be perfectly comparable if vial sizes or relative dosing forms (infusion, number injections from multi-dose vials, single use syringe injection) vary among countries and/or biologic products. Moreover, if rebates to government payers are not incorporated in the invoice data, nominal invoice prices could considerably overstate net of rebate payments; this might occur in the context of hospital tendering practices.[44] What is clear is that whether measured by standard unit or dollar shares, the diffusion of biosimilars among the four smaller EU countries is slowest in Belgium, followed by Norway, and generally most rapid in Finland and Sweden. Moreover, compared with Germany, the country adopting biosimilars most rapidly among the five largest EU economies, biosimilar adoption in Finland and Sweden is on a par if not more rapid and deep than in Germany.

European Relative Biosimilar/Brand Prices

Table 5 illustrates another surprising feature when comparing standard unit shares in Table 3 with dollar shares in Table 4: if for a given country/molecule/year the dollar share is greater than the standard unit share, then a logical inference is that the relative prices of the biosimilars appear to be *higher than* the reference and other branded products with which they compete. Table 5 shows the share changes between Tables 3 and 4—standard unit share minus dollar share. It shades in light grey those instances in which the standard unit share is smaller than the dollar share. This implies that the relative pricing of biosimilars might be higher, thus increasing

[44] We note, however, that in our nine country sample, for somatropin and filgrastim, only in Spain is dispensing limited to the hospital setting; in all other countries for these two molecules, dispensing occurs in both the hospital and retail setting. For erythropoietin alpha, in both Spain and Belgium dispensing occurs only in the hospital setting, and in all other countries dispensing takes place in both the hospital and retail settings.

Table 5 Biosimilar unit share minus dollar share of the molecular entity

	France (%)	Germany (%)	Italy (%)	Spain (%)	UK (%)	Belgium (%)	Finland (%)	Norway (%)	Sweden (%)
Somatropin									
2007	1	0	0	0	0	0	0	0	0
2008	2	0	0	0	0	0	−1	0	0
2009	2	0	−1	−1	0	2	−3	0	−2
2010	2	−1	−1	−4	0	3	−4	0	−4
2011	2	−1	−1	−5	0	3	0	0	−4
2012	2	−1	−1	−7	−1	2	−1	0	−5
Erythropoietin alpha and zeta									
2007	0	1	0	0	0	0	0	0	0
2008	0	10	0	0	0	0	−16	−1	−1
2009	0	7	0	0	−1	0	−55	−3	−2
2010	−1	4	2	10	0	0	16	−3	−3
2011	−1	0	3	17	1	0	3	46	−3
2012	−3	−4	4	13	−1	0	1	34	−3
G-CSF (*filgrastim*)									
2007	0	0	0	0	0	0	0	0	0
2008	0	0	0	0	0	0	0	0	0
2009	2	−14	0	2	1	0	0	13	0
2010	6	−21	2	7	0	0	4	−5	11
2011	7	−25	6	8	−2	0	4	−4	13
2012	5	−27	7	3	0	−1	11	11	6

Gray shaded means Unit Share is *less than* dollar share. This implies Biosimilars having *higher* prices

biosimilar dollar share. Alternatively, the analysis might be interpreted as indicating that standard units are imperfectly comparable across these products, or as noted earlier, the dollar shares exclude rebates from manufacturers to national/regional government authorities. Several patterns are worth noting, however. First, by country across all three products and 6 years, shaded cells occur for all nine countries, with half or more of the cells being shaded in Germany, the U.K., and Sweden. In France and Belgium, less than one third of the cells are shaded. Countries with between one third and one half of the cells being shaded include Italy, Spain, Finland, and Norway. Second, if one instead looks for molecule specific patterns, one finds that across the 6 years and nine countries, 33 of the 54 or 61 % of the cells are shaded for somatropin, for erythropoietin alpha and zeta, only 35 % of the cells are shaded, and for filgrastim the share of shaded cells is only 24 %. Hence, while the existence of biosimilar prices being apparently greater than for the branded competitors of the same molecule is widespread, it is particularly prevalent in Germany, the U.K. and Sweden, and for somatropin. Alternatively, this apparently counterintuitive finding concerning relative prices is observed least frequently in France, Finland, Norway and Sweden, and for filgrastim. It will be important for future research to focus on assisting researchers in understanding and interpreting these seemingly paradoxical pricing findings.

Several other characteristics of the EU biosimilar market merit attention, based on the IMS data. First, among the five largest EU countries, entry by biosimilar manufacturers is quite limited outside Germany. While Germany has multiple biosimilar entrants in all three products plus some cross-border shipments, Novartis/Sandoz is the only biosimilar entrant for two (somatropin and erythropoietin alpha) out of the three products in the other EU countries. With Germany again being the exception, since the early wave no new biosimilars have been entering these three product markets in the last few years. In most of the five largest EU countries the number of branded products outnumbers the number of biosimilar products by a factor of two or more. This market behavior contrasts with small molecule generics where multiple entrants over time are common.[45] This could reflect few other products losing their market exclusivity in recent years, but could also be indicative of the challenges of biosimilar entry, such as a preference for biobetters over biosimilars (e.g., long-acting Aranesp and Neulasta vs. short-acting biosimilars for erythropoietin/Eprex and filgrastim/Neupogen), particularly in countries such as Germany and Sweden.

The evidence from all nine EU countries demonstrates that at least for some products, biosimilars will be widely accepted by clinicians. The evidence further suggests that biosimilar usage in each country that chooses to allow them will be unique depending on the regulatory, reimbursement and clinical actions taken within each country. A somewhat surprising finding from this research is that at least up through 2012, in an ever more globalized therapeutic marketplace, biosimilar usage to date exhibits a distinctly local result for each product. Whether this is simply a differential initial market experience phenomenon with greater convergence and uniformity delayed but ultimately achieved, remains to be seen.

More generally, given differences in health care systems and cultures, biosimilar market development and share uptake may differ not only among the EU countries, but also in a systematic way between EU countries and the U.S. Although one could hypothesize that given the more litigious environment in the U.S., the FDA may decide to proceed more cautiously and require more clinical data than the EMA has in the past, the fact that the FDA approved Sandoz's enoxaparin sodium ANDA (referencing Sanofi's brand name Lovenox) without requiring any additional clinical evidence, whereas the EMA required additional clinical data to approve a biosimilar application for a low molecular weight heparin, seems to suggest that even such broad generalizations may not be valid.

Immunogenicity and INN Naming Implications for Biosimilar Adoption

Biological medicines have a higher risk than small molecule medicines of immunogenicity–being recognized by the body as "foreign" and inducing unwanted immune reactions.[46] As noted in European Commission (2013, pp. 32–33), immunogenicity

[45] Aitken et al. (2013), and Berndt and Dubois (2012).

[46] European Commission (2013, pp. 32–33).

is a significant safety element assessed by regulatory authorities considering approval of a new biologic, and is assessed in clinical trials by extensive testing and characterization of short and long term anti-product immune responses. Determining whether the original branded biologic and a potential biosimilar have similar short and long-term immune responses may take a considerable time and patient exposures. European regulators have often balanced this risk with granting patient access as early as legally possible by requiring extensive post-marketing risk management efforts. To the extent physicians, payers and patients are concerned about potential immunogenicity variations between the original branded biologic and the biosimilar, and potential emergence of immunogenicity after switching from the original branded biologic to the less costly biosimilar (and perhaps back), the pace at which the biosimilar is adopted may be diminished, limited perhaps only to new patients or to those not being satisfactorily treated by the original branded biologic and so unlikely to switch back to the original brand. Therefore, immunogenicity concerns may constrain biosimilar penetration more than for small molecule generics.

These immunogenicity concerns have created concerns whether approved biosimilars should have the same International Non-proprietary Name (INN) as the reference brand name biologic product or unique INNs recognizing the inevitably unique characteristics of each biologic product. For generic small molecules approved through an ANDA in the US or analogous application procedure in the EU, generics generally have identical INNs as their branded reference product. Although there are some exceptions (more on this below), for the most part brand-name drug makers and biotechnology manufacturers want biosimilars to have unique, non-proprietary or generic names to distinguish the medicines from the original biologics. From their perspective, distinct names would lessen confusion in the marketplace and via distinct product tracking and tracing through the product distribution channel process, would contribute to ensuring patient safety. For example, Geoff Eich, an Amgen spokesman, was quoted as stating "They should not all share the same name. I want to know which product was given the patient so I can work with the physician to understand what may have gone awry. We need distinguishable names because that's what tells us who to contact."[47]

Generic drug manufacturers, however, along with many pharmacies, health insurers, unions, pension plans and pharmaceutical benefit management organizations, disagree and believe that creating a new INN for biosimilars would, in fact, create confusion and inhibit adoption of lower priced medicines. They argue that pushing for distinct INNs is essentially a smokescreen and an attempt by branded biotechnology companies to blunt their revenue declines, especially in the lucrative U.S. market.[48] For example, Richard Davies, Hospira's chief commercial officer, has been quoted as saying, "Having the same name is clearly important for market uptake. We see the naming argument more around whether the products are different, but they're not…. Having the same name will help with market formation."[49]

[47] As quoted in FiercePharma (2014).

[48] Staton (2014).

[49] Staton (2014).

While much of this debate focuses on whether physicians would be more willing to substitute a biosimilar for the branded original if the two had identical INNs, and thereby contribute to lowering healthcare costs, there is also considerable disagreement about the extent to which distinct INNs would make it easier to identify, monitor and address safety issues. Monitoring via tracking and tracing biosimilars could be accomplished even when biosimilars had identical INNs, provided they had unique NDC codes, as well as information on lot number if these are also included in patient health records and prescription labels. Currently, while all small molecule generics have unique NDC codes they are not generally recorded and printed on each dispensed prescription. Alternatively, one could have a hybrid policy in which each biosimilar of a molecule had a common INN followed by a hyphen and the name or abbreviated name of the distributor.

The INN naming controversy has been particularly prominent recently in the U.S. For example, the Generic Pharmaceutical Association filed a citizen's petition with the FDA in September 2013 requesting that all biosimilars share the same INN as the original biologics. Brand name manufacturer Novartis, which has as a wholly owned subsidiary the generic manufacturer Sandoz, obviously has ambivalent concerns. Interestingly, in October 2013 the Novartis Group of companies filed a citizen's petition requesting that FDA "require that a biosimilar be identified by the same (INN)…as the reference product." Johnson and Johnson filed a petition arguing that biosimilar names should not be identical to the underlying biologic, and Amgen filed a massive 89-page document in December 2013 that detailed seven arguments supporting its case for distinguishable non-proprietary names.[50]

Amgen's position on INN naming conventions for a biosimilar is an interesting one, for it historically has been a major innovator biotechnology company, but currently is considering biosimilar entry. As Sanford Bernstein analyst Geoffrey Porges noted, "The company is clearly straddling two business opportunities that sometimes seem in conflict with each other—a defender of the innovative products and a participant in biosimilar products. That tension is going to continue to be difficult for them to manage".[51] Although it provided few details and specifics, Amgen announced in early 2013 it was planning to launch six biosimilars beginning in 2017—versions of four cancer drugs (Avastin™ Herceptin™, Rituxan™ and Erbitux™) and two rivals of Amgen's Enbrel franchise (Humira and Remicade). An Amgen spokesman hinted at the possibility of different launching strategies in the U.S. and emerging economies, thereby viewing biosimilars as more of an emerging market opportunity, stating "We feel that these medicines are very valuable and in many parts of the world patients have no access to them because they are expensive."[52] Bernstein analyst Porges expanded on this, saying, "They are a bellwether for the industry. The real focus is on getting into lower-priced markets and lower-priced products and driving business through cost efficiencies."[53]

[50] Karst (2013b),

[51] As quoted in Berkrot (2013).

[52] See footnote 51.

[53] See footnote 51.

An alternative interpretation of the Amgen strategy is that, given the substantial regulatory uncertainties in the U.S. and to a lesser extent in the EU, a risk diversification strategy focused on building low-cost, highly productive biologic manufacturing capacity might produce a higher return portfolio of biosimilar, innovator and biobetter products through differential pricing and distribution based on local market ability to pay and regulatory stringency. Might an attractive strategy be to gain approval for and market the same biologic formulation as a biobetter in the US (and perhaps Europe), but as a biosimilar in less wealthy and more price-sensitive regions of the globe?

Economic Incentives Facing Biosimilar and Biobetter Developers

The European experiences described above demonstrate that sufficient incentives already exist to induce some manufacturers to develop and introduce biosimilars. The experience also demonstrates, that with perhaps the exception of Germany, the number of biosimilar manufacturers for any specific biologic in a regulatory jurisdiction is generally less than five and sometimes limited to a single firm. For some products in some jurisdictions, the number of reference or other branded products significantly exceeds the number of introduced products. For instance, in France seven branded manufacturers have marketed somatropin since 2005 while only a single biosimilar somatropin, from Novartis, has been marketed since 2007. As noted in section "European Relative Biosimilar Volume Shares, 2007–2012" above, in some smaller EU countries such as Belgium and the Scandinavian countries of Finland, Norway, and Sweden the introduction of a single biosimilar under national contract has garnered significant share, presumably facilitated by national contracting. However, from the perspective of potential biosimilar manufacturers, the EU experience to date might suggest that the markets may support relatively few biosimilar manufacturers.

The reasons for the low numbers of biosimilar entrants cannot be inferred directly from the sales (standard unit and dollar share) evidence examined above. Some qualitative observations and resulting hypotheses can be made from the described development, regulatory and manufacturing processes as well as the immunogenicity phenomenon particularly relevant to biologics.

First, section "European Evidence on Biosimilar Uptake" above highlights that the EU biosimilar regulatory processes require substantial clinical development of at least one significantly sized trial. Recall that small molecule generics generally require no clinical trials conducted by the generic manufacturer, but only require very small bioequivalence studies based on cross-over designs. The US regulatory process for biosimilars also requires clinical trial evidence and moves further in distinguishing biosimilarity from interchangeability, with the latter requiring additional original clinical trial evidence from the biosimilar applicant. Qualitatively, a biosimilar manufacturer faces product development costs greater than those required of a small molecule generics manufacturer. The costs and risks, however, are quali-

tatively lower than those facing a novel pharmaceutical manufacturer. The biosimilar developer knows a priori that a reasonably replicated biologic will likely prove effective and incur similar safety risks as the reference product. These U.S. required clinical development investments entail multiple years, which from an economic valuation perspective delays and lowers, through discounting, the value of future profits. Compared to small molecule generics, it would appear that particularly U.S. biosimilar sponsors face greater development costs, time delays and some, albeit low, risk of clinical failure.

Second, section "European Relative Biosimilar Volume Shares, 2007–2012" above documents that biosimilar market share growth can reach levels at or above 80 %, (filgrastim in UK and Sweden, erythropoietin in the Scandinavian countries) but may also barely exceed single digit market shares even after multiple years of availability (somatropin in all examined countries). These represent relatively slow, low and variable clinical adoption rates compared to small molecule generics. It is not possible to determine from this data the extent to which physician and patient concerns about immunogenicity, interchangeability or simply true biosimilarity are responsible for the relatively slow EU market penetration by biosimilars. Other reasons such as branded product price reductions, continued sales and marketing efforts, and payer contracting delays may also reasonably play roles. Unlike the case for generic small molecules, national payers in EU countries have to this point not designated biosimilars as being fully interchangeable with their reference products. As a result, physicians may take a wait and see attitude as the biosimilar develops a track record, and thereby delay peak adoption of the biosimilar. Regardless of the detailed causes, it appears that biosimilar manufacturers face relatively low, variable and slow adoption which in turn should lower their financial expectations and enthusiasm for investment in biosimilars.

Third, as discussed in section "Manufacturing Distinctions of Biopharmaceuticals", biologic manufacturers traditionally face higher manufacturing costs than small molecules which could limit the downward pricing flexibility for biosimilar products. Section "Manufacturing Distinctions of Biopharmaceuticals" also notes that biologic manufacturing technologies have seen dramatic yield increases through improvements in production organisms and their growing conditions which lower costs per dose. In addition, new single-use manufacturing equipment is lowering the required capital costs and minimum efficient scale for biomanufacturing overall compared to the large, stainless steel tank production approaches of most biologic reference products. While each biologic product will face unique circumstances, it appears likely that biosimilar manufacturers, being free to adopt the newest technologies, should enjoy lower manufacturing costs than the reference products which should improve biosimilar expected financial returns.

Fourth, section "European Relative Biosimilar/Brand Prices" surprisingly indicated that biosimilar pricing may be close to or even higher than reference product pricing. The pattern was not consistent across countries or products and while the relative pricing may be similar, the absolute price level for the biosimilar products is likely lower than the branded pricing prior to biosimilar entry. Unlike with small molecule generics, at least some branded reference products attempt to defend their

markets through continued marketing and importantly, price reductions. While it appears that biosimilars may obtain higher relative pricing compared to generic small molecules, it is not guaranteed. In summary, it is not qualitatively clear that the potentially favorable biosimilar pricing offsets the challenges above.

On net, it is not clear whether biosimilar manufacturers can contemplate adequate financial returns in either absolute terms or relative to small molecule generic manufacturing. Compared to novel biologics, some factors are favorable to biosimilars: development is shorter, less costly and more likely to succeed; manufacturing costs are likely lower. However, other factors are not favorable: adoption appears relatively slow with highly variable peak market shares with likely lower pricing (although exceptions have been observed), and mandatory substitution through interchangeability designation has not been implemented. But in comparison to small molecule generics, nearly all the factors are less favorable, with pricing perhaps being the exception. These economic incentives, between those of novel therapeutics and generic small molecule medicines may help explain the relatively few observed biosimilar entrants in the EU. Generic small molecule manufacturers contemplating biosimilar entry may find the incentives insufficient to build the required extensive clinical development skills, especially if they perceive the financial outcomes directionally lower, more uncertain, or both. Novel therapeutic sponsors may find that the mixed incentives do not overcome their cultural preferences and operational infrastructure tuned for high risk, high commercial intensity and high margin therapeutics

Novel therapeutic sponsors may find the incentives for biobetters superior to those for biosimilars. Drug developers create biobetters by incrementally improving the pharmacologic or convenience characteristics of the reference product. For instance, developing an extended release version of the biologic through pegylation, which involves direct structural change to the molecule or through a formulation approach, may constitute a biobetter option. Biobetters are considered new products by regulators, requiring safety testing and clinical trials. However, since the underlying molecular biology and clinical performance of the reference product are well established, the safety testing can sometimes be streamlined and the clinical trial outcomes more easily predicted. Compared to a completely novel therapeutic, the development timelines are likely to be shorter and the clinical outcomes relatively low risk. The resulting time and cost savings improve financial returns for the investment. Upon commercialization, biobetters may be differentiated from the reference product, unlike biosimilars. This differentiation may allow for some pricing advantages for the biobetter and nearly always can provide a value rationale to the physician and patient for switching to the biobetter. Biobetter developers may therefore expect greater revenues from stronger pricing, larger ultimate market share and faster attainment of those larger shares. This approach of shorter, less expensive and less risky development resulting in a differentiable product for a known market may provide attractive risk-adjusted expected returns and so earn a place in the portfolio of a novel pharmaceutical firm. A possibly attractive mixed global strategy alternative, discussed earlier, would gain approval for and market the same biologic formulation as a biobetter in the US (and perhaps Europe), but as a biosimilar in less

wealthy and more price-sensitive regions of the globe, thereby taking advantage of newly available more efficient biologic manufacturing processes that reduce global production costs, but more importantly achieving differentiated product pricing with higher pricing and adoption rates in markets able to pay for the biobetter improvements while not forfeiting access to jurisdictions preferring only biosimilarity, with of course the usual *trans*-jurisdiction arbitrage shipment and public perception issues that such price discrimination strategies incur.

Some Final Observations on Other Issues Affecting Biosimilar Adoption

Notably, large traditional pharmaceutical companies as well as established innovator biotechnology companies have announced diverse strategies involving entry into the biosimilar/biobetter product spaces. For example, already in 2008 Merck announced a biosimilar development division Merck Bioventures with a commitment to invest $1.5 billion in which an initial target was a follow-on version of Amgen's erythropoietin-stimulating agent Aranesp™. Citing scientific complexities, Merck abandoned the Aranesp™ project in 2010, and instead focused on a follow-on to Amgen's multi-indication immunomodulator Enbrel™. A year later, in 2011 Amgen made a surprise announcement concerning a judicial decision that delayed considerably the patent expiration of Enbrel™, and shortly thereafter Merck Bioventures announced it was abandoning development of an Enbrel™ follow-on. Later in February 2013, Merck announced it was changing its strategy of developing follow-on biologics, and instead of going it alone Merck was reorganizing into a partnership with Samsung Bioepis, itself a joint venture formed by South Korean conglomerate Samsung and BiogenIdec; It also announced it was merging Merck Bioventures into a division of Merck Research Laboratories. In the Merck and Samsung Bioepis partnership, Merck ceded all development work to Samsung Bioepis, but gained exclusive global commercialization rights.[54]

The Samsung Bioepis joint venture was formed shortly before the Merck and Samsung Bioepis partnership announcement, and involved an agreement between Samsung Biologics, a newly minted development and manufacturing group, and BiogenIdec. Samsung officials initially described plans to develop a biosimilar to Rituxan™, a blockbuster treatment developed in partnership between BiogenIdec and Genentech, but at the December 2011 announcement of the formation of Samsung Bioepis, BiogenIdec officials went to some pains to make clear that Samsung Bioepis would not involve Rituxan™ or any of BiogenIdec's branded therapies. Within this joint venture, Samsung Biologics was responsible for sales and marketing, while BiogenIdec focused on manufacturing. According to BiogenIdec CEO George Stangos, "The manufacturing facilities have costs to run

[54] Carroll (2013a, b).

them, so the more products you run through them, the more efficient they are. To set ourselves up commercially could be a big distraction. I'd like a partner to take over that…This relationship will allow us to leverage our world-class protein engineering and biologics manufacturing capabilities, while maintaining focus on our mission of discovering, developing and delivering innovative therapies for patients worldwide"[55] A subsequent news story reported that two of the anti-inflammatory monoclonal antibodies targeted by the Samsung Bioepis joint venture were Remicade™ and Enbrel™.[56]

Although terms of the Samsung Bioepis joint venture did not allow it to pursue development of a biosimilar to Roche's Rituxan (marketed in the U.S. by BiogenIdec), in a separate alliance with the large contract research organization Quintiles, Samsung was able to attempt to develop a biosimilar to Rituxan™. In October 2012, however, a Korean newspaper reported that Samsung was halting development of its biosimilar to Rituxan™, because of "some internal reasons" speculated to involve difficulties in complying with recent regulatory guidance from the U.S. FDA. A Samsung spokesperson stated that Samsung was "speaking with FDA officials about clinical development requirements and a way forward for the SAIT101 program." Samsung's termination followed by about a month an earlier announcement by Israeli-based Teva that it was terminating its own late-stage development of a Rituxan™ biosimilar.[57] About 6 months later, in April 2013, Celltrion—another South Korean-based biotechnology company—and its partner Hospira announced the delay and potential termination of their late-stage development of a biosimilar version of Rituxan™. By mid-2013 both Teva and Samsung-Hospira had bailed out on their attempts to develop a biosimilar to Roche's Rituxan™, but observers have noted that other companies, such as Novarti's generic Sandoz unit and Boehringer Ingelheim, were continuing to pursue Rituxan™ biosimilars.[58] Although Samsung may have exited from development of a biosimilar to Roche's Rituxan™, Samsung has not gotten out of the biosimilar development business. In October 2013, Samsung and Roche announced they had clinched a "long-term strategic manufacturing agreement" whereby Samsung will manufacture an undisclosed number of Roche's cell-based products at its two manufacturing facilities in Incheon, South Korea.[59]

Another alliance announced with great fanfare in 2009 involved Israeli-based generic manufacturer Teva and the Swiss-based contract manufacturing firm Lonza Group, a Novartis subsidiary. Four years later, in July 2013, Teva and Lonza announced termination of the agreement to develop a series of biologics, including biosimilars. According to a Lonzo spokesman, "In our assessment those investments in biosimilars will require more capital than initially planned and will also take more time until they reach the market…This is why we intend in the future to

[55] As quoted in Carroll (2011).

[56] Carroll (2013c).

[57] McBride (2012).

[58] McBride (2013).

[59] Palmer (2013).

limit our role by focusing on our core expertise in the areas of contract manufacturing and cell line development." Rather than retreating from developing follow-on biologics, Teva vowed to continue developing them, stating that "Teva has a track record of success in the biologics arena and we plan to continue and build on that success."[60]

Interestingly, Teva has in fact been able to achieve some success with developing and gaining approval to market follow-on bioloigcs, not only in the EU but also in the US. However, success has been achieved not via the biosimilar pathway of the US's section 351(a) that allows applicants to use data from the innovative product to support their application, but instead via the recently enacted 351(k) provision by which Teva filed a traditional Biologics License Application (BLA). In October 2013 Teva received FDA approval to launch brand name Granix™ having the exact same recombinant active ingredient, filgrastic, as Amgen's Neupogen™; simultaneously, however, Teva withdrew its BLA for Lonquex, a long-acting pegylated version of filgrastim that Amgen markets under the US brand name of Neulasta™ and whose INN is pegfilgrastim. Neupogen™ is a once-daily medication, while Neulasta™ can be used less frequently on a once per chemotherapy dose regimen. Teva has another long-acting version of filgrastim, an albumin-fusion version, under BLA review at the FDA, which is called balugrastim. Because both the Granix™ and balugrastim applications are filed as BLAs, they are not subject to the biosimilar INN naming dispute, and therefore Teva has given them INNs of tbo-filgrastim and balugrastim. As noted earlier in this manuscript, Teva's Ratiograstim™, a filgrastim biosimilar, has been on the EU market since 2008 and its follitropin alfa biosimilar was just recently approved by CHMP in late 2013. In terms of the potential for Granix™ and balugrastim in the US market, analysts have noted that Amgen's Neupogen™ and Neulasta™ both are often on many pharmacy benefit plans' highest tier—number three or four. At a lower price, Granix™ and balugrastimc may stand a good chance of being listed on the second, "preferred", tier of those plans if they can overcome payer concerns of general overuse of the class in oncology, offering patients an opportunity to have a lower cost-sharing burden at a time when they will have many medical expenses.[61]

The diversity and volatility of strategies for follow-on biologics is striking. Presently there does not appear to be any observable convergence or dominant set of strategies. Although some firms exiting biosimilar alliances reference unexpected regulatory and capital cost developments, whether they are instead moving to a biobetter rather than biosimilar pattern is unclear. Predicting what will happen to biosimilars, biobetters, and other follow-on biologics in the US and EU is therefore speculative and highly likely to be inaccurate, particularly if a single theme is purported. It does appear likely that the extent of entry and decrease in price from branded innovator is likely to be much smaller than has been observed for generic small molecules in the US approved via ANDAs. Early indications are that the evolving market dynamics may be closer to what has been observed for injected

[60] As quoted in pmlive.com (2013).

[61] Gardner (2013).

specialty drugs that have been approved as AP-rated to the brand in the US. However, to date there has been little if any published research on the EU experience to confirm these preliminary observations and validate the analogy.

An alternative way to obtain insights on likely future follow-on biologic paths involves examining time paths of costs and revenues in simulation models comparing net present values of BLA/biobetter, biosimilar and entirely novel BLA paths for traditional molecules in selected therapeutic areas. Financial simulators driven by evidence based parameters can illustrate the range of incentives and challenges facing a drug developer considering an investment decision—whether that be in biosimilar, bio-better or a traditional novel therapeutic. Such evidence based simulations have been successfully employed to estimate the costs of drug development generally,[62] for therapeutic modalities,[63] for stratified medicine and companion diagnostic development,[64,65] and for adaptive licensing policy.[66] Beyond aiding individual firm investment choices, such simulations have informed public policy discussions regarding potential market inefficiencies in the drug development innovation chain, the effectiveness of the therapeutic innovation eco-system, and actions that might improve the level and productivity of therapeutic R&D investments. Similarly, further work on evidence based, financial simulators focused on biosimilar and biobetter market sub-segments could raise the level of public discussion regarding the future paths facing biologic therapeutics and point to the key externally observable evidence that might distinguish among competing perspectives and market dynamics. In addition since end of product life cycle revenues for a biologic or small molecule pharmaceutical often occur more than a quarter century after initial development, any differences among traditional novel compounds, novel biologics, biosiimilars and biobetters in the time at which significant events occur during the product life cycle—e.g., patent applications, regulatory filings, initiation of clinical trial phases and patient recruitment, FDA and EMA marketing approvals, launch and post-launch marketing efforts, initial loss of exclusivity (LOE), and extent and speed at which revenues are eroded post-LOE—can have significant impacts on net present value calculations. Note that the sensitivity of NPV calculations to differences among these molecule types in significant event timing will likely increase along with the choice of discount rate (that might also differ among traditional novel compounds, novel biologics, biosimilars and biobetters).

In summary, the biosimilar phenomenon is a relatively recent one involving complex options to develop, regulate, market and utilize biosimilars via an abbreviated BLA, biobetters via a BLA, or entirely novel but traditional small molecule medicines via NDAs. Understanding the historic and likely future evolution of these medicines will require addressing serious measurement issues involving volumes

[62] DiMaisi et al. (2003).

[63] DiMasi and Grabowski (2007).

[64] Trusheim et al. (2011).

[65] Trusheim and Berndt (2012).

[66] Baird et al. (2013).

and prices, and carefully analyzing descriptive market data trends for biologics and related specialty products in the EU, the US and other major global geographic regions, as well as how biosimilar adoption will alter incentives to develop biobetters or entirely new products.[67] But such understanding will also depend critically on simultaneously developing and implementing evidence-based financial, epidemiological, and clinical simulation models whose design, structure and underlying data are likely to differ substantially across therapeutic sub-segments.

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Appendix

Biologic Molecules with Biosimilar Entry in Europe and Elsewhere

Short-Acting Epoietin Recombinant (Erythropoietin, Alpha, Beta, Theta, Zeta)

According to the US Food and Drug Administration, "Erythropoietin is a glycoprotein whose main function is to stimulate the proliferation and differentiation of erythroid precursors in the bone marrow. Erythropoietin is produced mainly in the kidneys, though several other tissues produce lesser amounts of the growth factor."[68] Approved by the FDA on June 1, 1989, Epogen/Procrit (epoetinalfa) was produced in Chinese Hamster Ovary cells that have modified through recombinant DNA technology to encode the gene for human erythropoietin, and was initially approved for the treatment of anemia in patients with chronic renal failure. Epogen/Procrit was subsequently approved for the treatment of anemia due to ziduvodine therapy in HIV-infected patients (1991) and for the treatment of anemia in patients with non-

[67] According to Brennan (2014), as of June 2014 24 countries have established biosimilar pathways or have approved follow-on biologics.

[68] Epoietinalfa, June 24, 2011 Division Director Summary Review, STN BL 103234/5166, p. 5 of 38. Available online at Drugs@FDA.

myeloid malignancies whose anemia is due to the effect of concomitantly administered chemotherapy (1993). Both these supplemental approvals were based on demonstration of a reduction in the proportion of patients receiving shaded blood cell (RBC) transfusions.

Within Europe, the epoietin alpha reference product is Johnson & Johnson's Erypo or Eprex. As of June 2011, there were five approved biosimilar products: Binocrit (Sandoz/Novartis), Epo A (Hexal/Novartis), Abseamed (Medici), Retacrit (Hospira) and Silapo (Stada), all approved between August 28, 2007 and December 18, 2007.[69] Using the IMS Health classification scheme, there are two non-referenced products in the epoietin biosimilar accessible market (defined as an original product, granted market exclusivity at the start of its commercial life in Europe, whose exclusivity is now expired, with the product never have been referenced, or may have been referenced but the referencing biosimilar has not yet launched): Roche's NeoRecormon, and Teva's Eporatio/Biopoin.[70] In the U.S., in addition to having been approved by the FDA for treating anemia in cancer patients on chemotherapy, anemia in chronic renal failure patients, and anemia in zidovudine-treated, HIV-infected patients, epoietin alfa is approved for the reduction of allogenic blood transfusion in surgery patients. As of 2011, Epogen/Procrit was available in 2000, 3000 and 4000 units/ml 1 ml single-dose vials for subcutaneous injection or intravenous solution administration, in 20000 units/ml 1 ml multidose vials, in 10000 units/ml 1 ml single-dose and 2 ml multidose vials, and in 40000 units/ml single-dose vials for subcutaneous injection or intravenous solution administration.

Another erythropoietin stimulating agent (ESA) approved in both the US and EU is Amgen's darbepoetin alfa (brand name Aranesp in the US). Darbepoietin is distinguished from epoietin agents primarily because of Aranesp's longer serum half-life, implying generally less frequent dosing than the epoietins.[71] Currently Aranesp is patent-protected in the US and EU, with its earliest reported year of key US patent expiry being 2024; for Epogen this US patent expiry date is 2013.[72]

Growth Hormone for Children Born Small for Gestational Age—SGA (Somatropin Molecule)

Of the approximately 2.5 % of children who are born small for gestational age (SGA), 10–15 % fail to "catch up" by age two. Children who do not catch up by age two, if left untreated, are destined in many cases to have compromised final height, relative to the norm for the population. A relative height measure is SDS—the number of standard deviations an individual at a particular age is away from the

[69] Grabowski et al. (2013, p. 4).

[70] IMS Health (2011), slides 10, 11 and 40.

[71] Drug Facts and Comparisons (2011), p. 154.

[72] Grabowski (2013, slide 5).

age-specific population mean. Though there are differences across and within countries on the measure of SDS triggering treatment, growth hormone supplementation in children born SGA can enhance growth velocity, height SDS, and predicted adult height. Aside from the known adverse effects of growth hormone therapy, of concern in treating these children is a risk of accelerating bone age beyond chronological age, with the possibility of precipitating precocious puberty and compromising final stature on that basis.[73]

On August 24, 1995, the FDA approved Pharmacia and Upjohn's NDA # 020280 application for Genotropin (somatropin recombinant) for children born SGA who fail to manifest catch-up growth by 2 years of age, caused by an inadequate secretion of endogenous growth hormone. Over the years the FDA has approved a number of supplemental indications (e.g., growth failure associated with chronic renal insufficiency, with Noonan syndrome, with Prader-Willi syndrome, with Turner syndrome, in adults with either adult- or childhood-onset growth hormone deficiency, and others) as well as several related somatropin products, such as Omnitrope (Sandoz), Serostim (Serono), Humatrope (Eli Lilly), Nutropin (Genentech), Salzen (Serono), Tev-Tropin (Gate), HumatroPen (Eli Lilly), Zorbtive (Serono), Norditropin (Novo Nordisk), Accretropin (Cangene), and Nutropin AQ, Nutropin AQ NuSpin 5, NuSpin 10 and NuSpin 20 (Genentech). Most of these formulations are subcutaneous injection, lyophilized power for solution, although some products, such as Norditropin, involve pen or two-chamber cartridge delivery systems, with a reconstitution device used to mix the diluent and powder.[74] Somatropin must not be injected intravenously. Genotropin lyophilized powder contains somatropin of rDNA origin, a polypeptide hormone. The amino acid sequence of the product is identical to that of human growth hormone of pituitary origin (somatropin). Genotropin is synthesized in a strain of *Escherichia coli* that has been modified by the addition of the gene for human growth hormone.[75]

According to IMS Health, as of June 2011 both Pfizer's (who acquired rights with the acquisition of Pharmacia and Upjohn) Genotropin and Eli Lilly's Humatrope were reference products, the two approved biosimilar products were Novartis Sandoz' Omnitrope and Somatropin (unknown manufacturing laboratory), whereas the non-referenced products included Sanofi Aventis' Maxomat, Nova Nordisk's Norditropin, Ipsen's Nutropinaq, Merck Serono's Saizen, and Ferring's Zomacton.[76]

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[73] Genotropin, FDA Center for Drug Evaluation and Research, Application Number 20-280/S-031, Review—Administrative Documents, dated July 23, 2001. Available online at Drugs@FDA, Approval History, NDA 020280, 07/25/2001 031, p. 1 of 3, letter from David G. Orloff, M.D., Director, Division of Metabolic and Endocrine Drug Products to file NDA 20-280/S-031.

[74] "Somatropin", Drug Facts and Comparisons (2011), pp. 523–526.

[75] Genotropin Draft Package Insert, p. 3of 15, NDA 20-280/S-031, available online at Drugs@FDA, Approval History, NDA 020280, 07/25/2001.

[76] IMS Health (2011), slide 41.

Granulocyte-Colony Stimulating Factor (G-CSF), Filgrastim and Lenograstim Molecules

On February 20, 1991, the US FDA approved Amgen's filgrastim (trade name Neupogen) to decrease the incidence of infection, as manifested in febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever. On April 2, 1998, the FDA granted a supplemental NDA approval for acute myeloid leukemia (AML) adult patients receiving induction or consolidation chemotherapy, for reducing the time to neutrophil recovery and the duration of fever.[77] Other approved[78] uses of filgrastim include in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation, and for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.

Neutropenia is condition with an abnormally low number of neutrophils in the blood—the body's primary cellular defense system against bacteria and fungi. Neutrophils also help heal wounds and ingest foreign debris, such as embedded splinters. People who have severe neutropenia (fewer than 500 neutrophils per microliter of blood) can rapidly succumb to infection because their bodies lack the means to fight the invading organisms. Neutrophils mature in the bone marrow in about 2 weeks. After entering the blood stream, they circulate for about 6 h, searching for infective organisms and other intruders. When they find one, they migrate into the tissues, attach themselves to the intruders, and produce toxic substances that kill and digest the intruders. This reaction may damage healthy tissue in the area of the infection. The entire process produces an inflammatory response in the infected area, which appears on the body's surface as redness, swelling, and heat. Neutropenia has several causes. The number of neutrophils can decrease because bone marrow production isn't adequate or because large numbers of white blood cells are destroyed in the circulation. Aplastic anemia, and certain rare genetic diseases such as infantile genetic agranulocytosis and familial neutropenia cause decreases in the number of white blood cells. Certain drugs, especially chemotherapies used in cancer treatment, impair the bone marrow's ability to produce neutrophils. Growth factors that stimulate the production of white blood cells, particularly granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) can eliminate neutropenic episodes in cyclic neutropenia.[79]

In the U.S., Neupogen is still marketed exclusively by Amgen. Four dosage forms are approved—two in single use vials, and two as pre-filled injectable syringes.

[77] Neupogen, "Review and Summary Basis of Approval", Application Number 103353/000, Center for Drug Evaluation and Research, February 20, 1991. "Supplement 1036, Letter, April 2, 1998. Available online at Drugs@FDA.

[78] "Filgrastim", Drug Facts and Comparisons (2011), p. 163.

[79] "Neutropenia", in White Blood Cell Disorders, ch. 158, in Robert Berkow, Editor, *The Merck Manual of Medical Information*, (Home Edition), Whitehouse Station, NJ: Merck Research Laboratories, 1998, pp. 761–763.

Neupogen is produced by Escherichia coli (E coli) bacteria into which has been inserted the human granulocyte colony-stimulating factor gene. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA analysis, except for the addition of an N-terminal methionine necessary for expression in E coli. Because Neupogen is produced in E coli, the product is non-glycosylated and thus differs from G-CSF isolated from a human cell. Neupogen is a sterile, clear, colorless preservative-free liquid for parenteral administration. In order to maintain clinical benefit, chronic daily administration is required.[80]

A second form of recombinant human granulocyte colony-stimulating factor is lenograstim (brand name Granocyte, Chugai Pharmaceuticals, marketed in the EU by Sanofi Aventis), a Chinese hamster ovary-derived G-CSF, indistinguishable from native G-CSF, and differing from filgrastim which is an Escherichica coli-derived G-CSF and is non-glycosylated, having an extra methionine group at the N-terminal end of the peptide chain.[81] Granocyte (lenograstim) is not available in the U.S., but is a non-referenced product in the EU, having brand names in addition to Sanofi Aventis' Granocyte, Euprotin (Almirall), Myelostim (Italfarmaco) and Roche's Neutrogin. As of June 2011, a number of biosimilars were approved in the EU using Amgen's filgrastim (Neupogen) as the reference product. These biosimilars include a Biograstim (CT Arzzneimittel), Novartis'/Sandoz filgrastim Zarzio, Teva's Tevagrastim, Ratiopharm's Ratiograstim, Hexai's Filgrastim Hexal, and Hospira's Nivestim, all approved between September 15, 2008 and June 8, 2010.[82]

Neulasta (pegfilgrastim) is a second-generation injectable granulocyte colony stimulating factor approved in both the US and EU. Pegfilgrastim is distinguished from filgrastim agents primarily because of pegfilgrastim's longer serum half-life, implying generally less frequent dosing than the filgrastims. Specifically, whereas filgrastim requires daily dosing, pegfilgrastim is administered only once per chemotherapy cycle.[83] Currently Neulasta is patent-protected in the US and EU. According to Grabowski (2013, Slide 5), while the earliest reported year of key US patent expiry is 2013 for Amgen's Neupogen, for its Neulasta it is 2015.

Infliximab (Remicade)

The EMA's Committee on Human Medicinal Products (CHMP) approved Hospira's biosimilar application for infliximab (injection) on September 10, 2013 with Centocor's (Johnson & Johnson) Remicade serving as the reference product. Infliximib is a monoclonal antibody, an immunomodulator distributed as a

[80] "Neupogen (Filgrastim) Drug Information: User Reviews, Drug Side Effects…", p. 1 of 3 in RxList…, last reviewed June 4, 2012. b Available online at http://www.rxlist.com/neupogen-drug.htm.

[81] Kim et al. (2003), p. 1 of 14.

[82] IMS Health (2011), slide 42. According to Grabowski et al. (2013, p. 4), Ratiopharm's Filgrastim ratiopharm was approved by the EU on September 15, 2008, but was withdrawn on July 20, 2011.

[83] "Pegfilgrastim", Drug Facts and Comparisons (2011), p. 166.

lyophilized powder for solution. In the EU it is approved for treating ankylosing spondylitis (a chronic inflammatory disease of unknown origin, first affecting the spine and adjacent structures and commonly progressing to eventual fusion of the involved joints[84]), psoriatic arthritis and psoriasis (see Table 1 in main text). In addition to these three indications, in the U.S. infliximab (Remicade) is approved by the FDA for treatment of Crohn disease, fistulizing Crohn disease, rheumatoic arthritis, and ulcerative colitis.[85] Infliximab is the first monoclonal antibody approved as a biosimilar in the EU. Like several other immunologic agents, infliximab has a risk of serious infections, since patients treated with infliximab are at an increased risk for developing serious infections that may lead to hospitalization or death. According to Drug Facts and Figures (2011, p. 2822), "Most patients who developed those infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids."

Since EMA approval of biosimilar infliximab (referenced to Remicade) occurred just several months ago, data on its uptake within EU countries are not yet available. Indeed, it is likely that Hospira has not yet obtained reimbursement approval from any of the EMA member countries.

Follitropin Alfa (Gonal-F)

The EMA's Committee on Human Medicinal Products (CHMP) approved Teva's biosimilar application for follitropin alfa (injection) on September 27, 2013 with Merck Serono's Gonal-F serving as the reference product. Follitropin alfa is a human follicle stimulating hormone (FSH) distributed as a sterile, clear solution for subcutaneous injection. In the EU it is approved for treating an ovulation (the failure of the ovaries to release an egg during an ovulation cycle[86]), stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies (ART) such as in vitro fertilization (IVF), gemete intra-fallopian transfer and zygote intra-fallopian transfer, and for ovaleap in association with a luteising hormone (LH) preparation for women with severe LH and FSH deficiency. It is also approved in the EU for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotropic hypogonadism with concomitant human chorionic gonadotropin (hCG) therapy.[87] In the U.S. follitropin alfa FDA approved indications are limited to an ovulation and ART treatments.[88] Follitropin alfa is the first fertility biosimilar approved in the EU.

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[84] "Ankylosing spondylitis" in Anderson et al. (1998), pp. 94–95.

[85] Drug Facts and Figures (2011), pp. 2822–2823.

[86] "Folliropin Alpha" Drug Facts and Comparisons (2009), p. 350.

[87] European Medicines Agency (2013c).

[88] Food and Drug Administration (2014a).

Since EMA approval of biosimilar follitropin alfa (referenced to Gonal-F) occurred just several months ago, data on its uptake within EU countries are not yet available. Indeed, it is likely that Teva has not yet obtained reimbursement approval from any of the EMA member countries.

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