Biosimilars: Theory, Empirics, and Policy Implications

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1 Introduction

A biosimilar pharmaceutical is a close, but not identical, copy of an approved biologic branded product. It is known as a biosimilar, rather than a biogeneric, because current technology does not allow for making an exact copy of a large molecule drug. Exact molecular copies can be made in the case of small molecule drugs; these are known as generics and have enjoyed a simple pathway to regulatory approval in the United States for 30 years. Biosimilars are not available in the United States, but they are regulated – and several are approved and sold – in Europe. The Patient Protection and Affordable Care Act instructed the U.S. Food and Drug Administration (FDA) to create a pathway for approval of biosimilars in 2010, but at the time of writing, the FDA had not yet finalized the rules for regulatory approval of Biosimilars in the United States. One reason may be that the scientific issues are complex and changing. The tests, for example, that a manufacturer can perform to demonstrate its product is very similar to the reference product are improving every day. Another reason one might imagine for the lack of progress on a pathway is that branded biologics would prefer not to face competition. Such a firm might find it in its interest to lobby to slow adoption of rules allowing biosimilars. The result is a situation where policy-makers and economists in the United States can learn from the seven years of market experience of biosimilars in Europe.

In the United States there are two main concerns expressed by those opposed to biosimilars. The first is that because biosimilars are not an exact copy of the original drug, it is possible that the biosimilar product won't be safe for patients. It is difficult to set scientific standards for what constitutes "similar" (or more specifically, similar enough) in a way that protects patient safety, but that is also feasible to achieve by manufacturers once safety standards are met. The second concern is an economic one. The idea is that the nation will not in the end benefit (much) from biosimilars because they are not exact copies of brands and therefore not perfect substitutes. This in turn means that biosimilars may not create price pressure on the branded product the way that the introduction of a standard generic drug is known to do. As a corollary, the entry of a biosimilar may not cause

prices to fall in the way we have become accustomed to with small-molecule generics because patients and physicians won't consider it to be a substitute. Moreover, the marginal cost of production of a biologic is much higher than that of a small-molecule drug. Therefore, even if robust price competition were to arise, it would not be expected to drive price down as much as commonly seen in small molecule markets. This paper will address the second of these critiques: how much price competition do biosimilars create?

The biologics market represents X% and Y% of total expenditure on pharmaceuticals in Europe and the United States, respectively. In the United States, pharmaceutical constitutes Z% of total healthcare costs. What is particularly noteworthy about biologics is their typically high unit price, small market size, and high rate of growth. Many diseases treated by biologics are rare, and consequently market sizes are quite small. The prices of these drugs are typically high partially because the cost of manufacture is high, partially because the disease being alleviated is often very serious, and partially because R&D costs cannot be recouped on a small number of patients unless prices are high. The growth rate of expenditure on biologics is roughly 12% per year – much higher than the rest of pharmaceutical spending (which is close to flat in the United States).

This paper outlines the theoretical and regulatory issues surrounding biosimilars. It goes on to document the experience in Europe of biosimilar approval and entry. The European Medicines Agency (EMA) provides a single scientific and regulatory body that must approve all biologic products sold in the EU. However, even though testing and approval is centralized, each country has its own reimbursement policies. Parties that wish to market and sell their drugs in Europe must first negotiate a price with the health authority in each nation. Thus there is heterogeneity across countries in terms of initial biologic price and usage, as well as biosimilar prices and penetration.

The price and share outcomes for biosimilars across European countries are dramatically different. The second part of the paper explores the reasons behind these differences. Policies on procurement and pricing of biosimilars vary greatly across countries. We show that the existence and identity of the residual claimant in the procurement process – namely

the party who saves money when the biosimilar is dispensed – is critical to understanding the penetration of biosimilars and cost savings from their use.

2 Background

2.1 Biologics

Biologics, also called "biopharmaceuticals" or "biologic drugs" are a broad class of products including, but not limited to, vaccines, somatic cells, gene therapies, and recombinant therapeutic proteins. The FDA notes that drugs classified as biologics may be composed of molecular structures ranging from sugars, to proteins, to nucleic acids – or a combination of these substances and may also include living cells or tissues.[1] Biologics are typically derived from living organisms or microorganisms and typically require intensive manufacture through biological processes. Biologics are widely used to treat serious and life-threatening diseases such as cancer, diabetes and rheumatoid arthritis. The FDA notes that "biological products often represent the cutting-edge of biomedical research and, in time, may offer the most effective means to treat a variety of medical illnesses and conditions that presently have no other treatments available."[2]

Biologics are large, complex, and heterogeneous proteins with molecular weights ranging from 18,000 to 45,000 Daltons (GaBI, 2012); by contrast, small molecule drugs typically have molecular weights of just a few hundred Daltons. Unlike chemical drugs, which have a known molecular structure, most biologic drugs are so large and complex that they are difficult to identify molecularly. The active substance of a biological is typically a collection of large protein isoforms and not a single molecular entity. This fact makes manufacturing of biologics of all kinds much more of a challenge than producing traditional small molecule branded drugs or generics.

[1] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm
[2] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm

2.2 Biologic drug development and the market for biologics

The R&D process for new biological entities (NBEs) has several special characteristics. NBEs often originate in VC-financed startups which themselves have significant uncertainty. Additional sources of risk in the clinical trial process include – but are not limited to – issues related to formulation or dosing and manufacturing scale-up. Manufacturing know-how and process specifications are considered critical elements for the successful production of NBEs. Higher risks associated with the development of new biologic agents have been confirmed by several studies; these include such issues as lower Phase III success rates than chemical drugs.

Moreover, development times for new biologic therapies are quite long – typically over a decade – and development costs are high. Development costs are likely comparable in overall magnitude to estimates of the cost of developing new chemical drugs,[3] but cost components are very different: biologics development is characterized by higher discovery and preclinical expenditures, longer mean clinical development times and higher costs associated with process engineering and manufacturing (Grabowski, 2008; Grabowski et. al., 2006).

Distribution systems for biologics and chemical drugs also differ dramatically: while most drugs are oral agents and can be distributed through retail and mail-order pharmacies, biologics are typically delivered directly in a hospital, a clinic, or a physicians office.[4]

Biologics represent the fastest growing segment of the pharmaceutical market: in recent years, biologics growth has been nearly double that of total pharmaceutical growth (GaBI, 2012; IMS Health, 2011). Indeed, in 2010, seven of the top 20 drugs in the US were biologics (Lancet, 2012). By 2015, worldwide sales of bio*similars* (follow-on biopharmaceuticals) are expected to reach between US$1.9 and $2.6 billion, as compared to $378 million in the year leading up to mid-2011 (IMS Health, 2011). It is this growing market for biosimilars that is considered in this paper.

[3]DiMasi and Grabowski (2007) look at R&D costs for a sample of recombinant proteins and monoclonal antibodies and confirm that some phases of the development process (e.g. manufacturing) are more costly, but that "estimated total capitalized cost per approved new molecule was nearly the same for biopharmaceuticals as [chemical drugs]."

[4]However, a few self-injectable products are also dispensed through pharmacies

2.3 Biosimilars

Biosimilars differ from "true generics" in terms of their physical characteristics as well as in how they are regulated. Generic versions of chemically manufactured small molecules are based on bioequivalence – containing the same quantity of active substance(s) as the reference medicine. These generic drugs can be used in the same dose to treat the same disease with equal expected efficacy. Biosimilars, on the other hand, are much larger molecules and so follow-on products, such as biologically manufactured recombinant proteins, are based on similarity to a reference product rather than proof of identical molecular structure (Manheim et. al. 2006; Rovira et. al., 2011).

2.4 Data exclusivity and regulatory issues

2.4.1 Europe

The European Medicines Agency (EMA) regulates biologics and other drugs in the European Union. Europe provides data exclusivity under the "8+2+1" regime on all products submitted for approval on or after October 30th, 2005. Under this regime, both new chemical entities (NCEs) and new biologic entities (NBEs) are granted ten years of market exclusivity (8 years of data exclusivity + 2 years of additional marketing exclusivity). An additional year of data exclusivity is provided for products with "significant" additional indications that are approved within 8 years after a product comes to market.

The EMA is responsible for regulating the manufacturing as well as analysis of biosimilars to assess comparability with reference products. In the case of biosimilars, new products must meet much higher approval requirements than those of generic small-molecule drugs. These include presenting results from pre-clinical and clinical trials, to demonstrate safety conditions during production and safety and effectiveness of the drug itself, respectively. Guidelines concerning scientific data to substantiate the claim of similarity are issued by the Committee for Medicinal Products for Human Use (CHMP). Complicating matters further is the fact that there is heterogeneity across therapeutic groups and products in

proving product comparability and subsequent safety. Indeed, CHMP notes that "parameters such as the three-dimensional structure, the amount of acido-basic variants or post-translational modifications such as the glycosylation profile can be significantly altered by changes, which may initially be considered to be minor in the manufacturing process. Thus, the safety/efficacy profile of these products is highly dependent on the robustness and the monitoring of quality aspects" (CHMP/437/04). Such issues are not relevant and such regulatory measures are not necessary in generic approval, which simply requires demonstrating bioequivalence of drug content and concentration.

The specific requirements for a biosimilar Marketing Approval Application (MAA) dossier are articulated in Annex I to Directive 2001/83/EC and must satisfy the technical requirements of the monographs of the European Pharmacopoeia and any additional requirements (e.g. those defined in relevant CHMP guidelines). The requirements of a new biosimilar application include all of the following:

- Administrative data
- Summary of product characteristics
- Expert reports
- Qualitative and quantitative particulars of the constituents.[5]
- Description of manufacturing method
- Controls of starting materials
- Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
- Control tests carried out at intermediate stages of the manufacturing process
- Control tests on the finished product (including general characteristics of the finished product, identification and assay of active substance(s), identification and assay of excipient constituents, safety tests)

[5]Active substances present in the form of compounds or derivatives shall be designated quantitatively by their total mass, and if necessary or relevant, by the mass of the active entity or entities of the molecule. For allergen products, the quantitative particulars shall be expressed by units of biological activity, except for well defined allergen products for which the concentration may be expressed by mass/unit of volume.

- Stability and toxicity tests
- Examination of reproductive function and embryo/foetal and perinatal toxicity tests
- Tests of mutagenic potential, carcinogenic potential
- Data on pharmacodynamics and pharmacokinetics
- Local tolerance tests
- Well-established medicinal use
- Conduct of trials
- Presentation of results
- Clinical pharmacology
- Bioavailability/bioequivalence
- Clinical efficacy and safety
- Documentation for applications in exceptional circumstances
- Post-marketing experience
- Well-established medicinal use

The European Generic Medicines Association (EGA) defines two terms: 1) interchangeability (the doctor's ability to prescribe a biosimilar instead of a reference product) and 2) substitutability (a pharmacist can substitute a biosimilar at the time the product is dispensed).[6] The extent to which biosimilar products products can/should be interchangeable and/or substitutable remains open to discussion, however many European countries have expressed opposition to automatic substitution by pharmacists and both France and Spain have passed legislation to ban automatic substitution without express permission of the prescriber under the argument that biosimilars do not fall under the definition of generics (Rovira et. al., 2011).

[6]The United States uses the same terms with respectively opposite definitions.

2.4.2 Australia

Australia also has a regulatory pathway for biosimilar entry and will be included in some of the analyses below. Australian biosimilars are regulated by the Department of Health's Therapeutic Goods Administration (TGA), which borrows much of its regulatory policy from EU guidelines.

As in the EU, the TGA defines a biosimilar or similar biological medicinal product (SBMP[7]) as a version of an already registered biological medicine that a) has a demonstrable similarity in physicochemical, biological and immunological characteristics, efficacy and safety, based on comprehensive comparability studies and b) has been evaluated by the TGA according to this guideline and other relevant EU guidelines adopted by the TGA.[8]

Indeed, the Australian data requirements specific to biosimilars are based almost entirely on those outlined in a number of EU guidelines as well as an International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline on the assessment of comparability. Additionally, the TGA requires the submission of a limited number of Australia-specific administrative documents.[9] A full list of EU guidelines that have been adopted by the TGA for the approval of biosimilars can be found in Appendix X,[10]

[7]Although referred to as biosimilars in Australia, the term 'similar biological medicinal products' (SBMPs) is derived from the EU guidelines adopted by the TGA. The terms may be used interchangeably. In other jurisdictions, they also are variously referred to as: similar biotherapeutic products (WHO), follow-on biologics, and subsequent entry biologics.

[8]http://www.tga.gov.au/industry/pm-argpm-biosimilars-00.htm

[9]These include a Pre-Submission Planning Form (PPF), information for sponsors completing the PPF, mandatory requirements for an effective application, general submission dossier requirements, and a risk management plan guideline

[10]Adopted docs: CHMP/437/04: Guideline on similar biological medicinal products; EMEA/CHMP/BWP/49348/2005: Guideline on similar biological medicinal products containing Biotechnology-Derived Proteins as Active Substance: Quality Issues; CPMP/ICH/5721/03 ICH Topic Q 5 E: Comparability of Biotechnological/Biological Products Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process; EMEA/CHMP/BMWP/42832/2005: Guideline on similar biological medicinal products Containing Biotechnology-Derived Proteins as Active Substances: Non-Clinical and Clinical Issues; CHMP/BMWP/101695/2006: Guideline on Comparability of Biotechnology-Derived Medicinal Products after a change in the Manufacturing Process - Non-Clinical and Clinical Issues; EMEA/CHMP/BMWP/14327/2006: Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins; Product-specific guidelines detailing the clinical and safety data requirements.
(http://www.tga.gov.au/industry/pm-euguidelines-adopted-clinical.htm) but policies and standards are

2.4.3 The United States

At present, most biologic therapies available in the US are regulated through the Public Health Service Act, which does not have a provision for "follow-on" versions of biologics, (biosimilars) – that is, there is no analog to generic chemical drugs as provided for under the Hatch-Waxman Act, which grants a (5 - 7.5) year data exclusivity period for NCEs. With the exception of some early biologics like human growth hormone (hGH), insulin, and conjugated estrogens, which were approved as drugs under the federal Food, Drug, and Cosmetic Act (FD&C Act), biologics in the United States are regulated separately from chemical drugs by the Center for Biologics Evaluation and Research (CBER) of the FDA.

At present, the FDA is considering how it will regulate follow-on biological products in the future. The FDA has not yet defined the parameters of the regulatory approval process for biosimilars, however an abbreviated regulatory pathway was created by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act), which was enacted on March 23, 2010, as part of the Patient Protection and Affordable Care Act.

On February 9, 2012, the FDA issued three draft guidance documents on biosimilar product development (FDA, 2012). The first of these addresses "scientific considerations in demonstrating biosimilarity to a reference product" and is intended to help sponsors of biosimilars demonstrate that "a proposed therapeutic protein product is biosimilar to a reference product for the purpose of submitting an application under 351(k) of the PHS Act to the FDA" (henceforward a "351(k) application"). The second document addresses "quality considerations in demonstrating biosimilarity to a reference protein product," while the third deals with "questions and answers regarding implementation of the BPCI Act" (FDA, 2012).

The FDA is currently accepting public comments on its draft guidance documents and there remains a fair amount of debate as to what FDA will require of biosimilars – in particular with respect to requirements to prove interchangeability. In a recent editorial, The Lancet urged the FDA "to integrate the data, experience, and lessons learned by the

generally the same as those employed in the European Union

European Medicines Agency, which has approved a dozen biosimilars since 2006" (Lancet, 2012).

2.5 Policy considerations: biosimilars

Often referred to as "the Hatch-Waxman Act," the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman) was landmark in establishing the Abbreviated New Drug Application (ADNA) process for generic drug approvals. With the size of the generic pharmaceutical market now reaching over 50% of US prescription pharmaceutical market by volume, Hatch-Waxman has been successful in both increasing generic entry and slowing drug price growth. Of great interest in the current policy debate are the questions of a) whether and b) the extent to which biologics can be treated like pharmaceuticals with respect to the production of generic compounds.

As regulatory guidance to govern the exclusivity period for new biologics is considered, there are several important factors to keep in mind. Optimal exclusivity times are important and the usual theories apply: there will be tradeoffs between incentives for new product development vs. price competition. As a corollary, in industries that have costly and risky R&D processes (such as biologics), longer exclusivity periods will be required to realize innovation benefits.

Given the tremendous R&D costs associated with developing new biologics, the intellectual property associated with a biologic therapy is of great value; any legislation governing follow-on biologics and data exclusivity will have a meaningful impact on assessments of risks, rewards and value of biologics and biosimilars for private and public markets. Previous analyses of break-even lifetimes (e.g. Grabowski, 2008) have highlighted that all economic models are very sensitive to assumptions about the cost of capital. Complicating the policy decision further is the reality that the extent to which manufacturing costs will decline over time as biosimilars become available is largely unknown[11].

[11]Grabowski et. al. (2006) note that: "Over longer time frames, expansion in manufacturing capacity and technological advances in process engineering could greatly decrease the fixed and variable costs for follow-on biologics. In particular, a new group of follow-on manufacturing "specialists" might emerge, which might

Moreover, market authorization for biosimilars demands a costly and detailed clinical development process and does not necessarily ensure substitutability with the reference product (Rovira et. al., 2011). Unsurprisingly then, the European experience with biosimilars has suggested that the market penetration of follow-on products is lower than what one would expect from generic drugs, but that given the very high prices of patented biologic therapies, it may still be the case that small price reductions could trigger meaningful reductions in spending (Rovira et. al., 2011).

This paper will address the European experience in detail and present findings from the introduction of biosimilars on subsequent take-up, prices, and quantities of biosimilars sold. We introduce variation in country-level institutions to identify policy lessons from the European experience and discuss policy implications for the United States.

3 Conceptual Framework

3.1 Previous studies of biosimilar entry

Grabowski et. al. (2007) "analyze market entry and prices in the generic biologic market using a theoretical model of generic biologics and regression estimates from generic pharmaceuticals." Noting that a) large markets are more likely to have more entrants (as in Scott Morton, 1999) and that b) firms consider fixed costs, variable costs, and market size in considering market entry, the authors construct a model of monopolistic competition, in which the ratio of generic price to pre-entry monopoly price is the key dependent variable. They find that the number of generic pharmaceutical manufacturers will be increasing in total market size and decreasing with restrictions on product use and that generic price will be closer to the branded product's price when there are fewer entrants. Further, the authors

be biotech product firms, manufacturing technology platform firms, or established generic manufacturersExpanded roles for outsourced manufacturing specialists could emerge, just as contract research organizations (CROs) have "hollowed out" some aspects of clinical development, if they are able to lower manufacturing costs for biologics." The authors emphasize that while competition in process technology may improve market access, drive down costs, or stimulate entry, it is hard to know how – and indeed, whether – these gains would be passed on to patients and/or payers.

believe that the production of generic biologics will have substantially higher fixed costs from clinical testing, capital costs and manufacturing than is the case for generic chemical drugs and. As such, they estimate that there will be less entry than what has been observed in the pharmaceutical market. As a direct result, price competition from biosimilars will be limited and the potential for price-reduction will be less than that in the pharmaceutical market.

A small and nascent body of research has considered the impact of the introduction of biosimilars into the European market, by far the most advanced market with 80% of global spending on biosimilars (IMS Health, 2011). Rovira et. al. (2011) estimate that biosimilars' market value grew from 33 million Euros in 2007 to 65 million Euros in 2009, which corresponded to an increase in market penetration of biosimilars from 0.34% to 6.64%. The authors find that following biosimilar introductions, biosimilar prices, on average, were between 10 and 35% lower than their respective reference products[12].

3.2 Framework for this study

There are two types of models we will draw on in this paper. The first is classic entry literature such as Bresnahan and Reiss (XX) and Berry (XX). These authors emphasize that entry will occur when it is a positive-profit project, and therefore the market must be large enough to accommodate the entrant at a competitive scale. This concept has been operationalized in a pharmaceutical context by Scott Morton, who looks at the entry of generic drugs in the United States. Entry is more likely in larger markets, and is more likely when the characteristics of the entry opportunity match the capability of the entrant. For example, a firm specializing in injectable drugs will be more likely to enter an injectable market than a market for pills. Likewise a firm with significant sales in cardiovascular diseases will be more likely to enter a new cardiovascular market. We see similar patterns in biosimilars; firms with appropriate distribution channels and manufacturing expertise are entering biosimilar markets.

[12]Rovira et. al. (2011) also provide a country-by-country summary of substitutability, availability, pricing and reimbursement in the following European Union countries: Italy, Spain and the UK as well as partial information for Germany, Hungary and Norway.

The analysis of the entry of biosimilars will be a little bit different than that of small-molecule generics because of their cost structure and level of differentiation. An early paper by Graboswki (XX) laid out these issues. First, higher marginal costs mean that price competition will not lead to as low prices as in chemical generics. Second, similarity rather than perfect substitutability means that consumers will not respond as elastically to price differences. We see the arrival of biosimilars in different markets and countries over time, and we assume these models are guiding those decisions.

The second set of concepts we use in the paper are models of procurement, and incentives in procurement. We will focus the motivation of our framework here on the case of the hospital's use of biologic drugs, as that is an important setting for our three molecules in Europe. Healthcare in Europe is public in either its provision or funding. Therefore the buyer of biosimilars, the hospital, is a non-profit regulated firm. There is a substantial theoretical literature in economics that investigates the motivation of the organization to purchase the lower cost input. Our basic benchmark is the distinction between cost-plus regulation and fixed price. The hospital could be paid the costs it incurs to treat all the patients who arrive in a given time period. The manager of such a hospital would experience no difference between using the reference biologic and a less expensive biosimilar. In contrast, under a fixed-price system the hospital would be paid some amount for a procedure or diagnosis and would subtract its costs from revenue to determine its surplus.

The classic work of Averch and Johnson (1962) demonstrates this issue. In a setting in which the regulator has asymmetric information concerning next year's cost, it cannot perfectly instruct the regulated firm how to choose inputs. The managers of the firm have preferences not to exert effort, though effort reduces costs. For example, effort might involve creating and running a tendering process for biologic drugs at the hospital. As in Laffont and Tirole,[13] the regulator doesn't know the hospital's cost because it does not realize the benefit of creating a tendering process, while the managers of the hospital do. If the regulator pays the firm a fixed price contract then managers will exert effort to lower costs up to the point where marginal disutility of effort is equal to the marginal utility from the cost savings. It

[13] *A Theory of Incentives in Procurement and Regulation* (1993 MIT Press)

is interesting to think about what this utility from cost savings might be in our setting.

How would the manager of a hospital spend such savings? One option is that the government takes the funds back in a subsequent period; this would reduce any incentive on the part of the manager to exert effort to lower costs. A second option is that the manager spends the savings on a nicer office or similar projects that do not benefit consumers. Thirdly, the manager might use the cost performance of the hospital to advance his career.

A fourth option that fits the healthcare setting well is to imagine the manager uses the savings to offer other healthcare services at the hospital. Perhaps such a manager has internalized the mission of the hospital and chooses the marginal project that has most net benefit to consumers. Notice that in such a setting the central healthcare authority does not have the information or ability to control the hospital's activities and set them optimally. For example, if the central authority had identified the social costs and benefits of each procedure, it could give a list of approved socially-valuable services to the hospital. In such a world if the cost of a biologic drug fell, it is not clear the center would want the hospital to choose to provide additional services rather than remit the savings to the taxpayer. However, the setting we envision has an imperfectly-informed center. While there is a considerable theoretical literature showing how each of these incentives might operate (See Dixit, Tirole, Holmstrom, Gibbons, etc.) there is little the literature offers on which of these forces is empirically operational in particular sectors such as healthcare.

That center may rely on mission-driven managers to use cost savings to the benefit of patients. Or the center may run the auction for the entire country and not allow for the hospital to have any discretion over its inputs. On the other hand, the center may not choose a fixed-price regulation at all, but pay the hospital's costs. In this paper we focus on the impact that the choice of regulation has on biosimilar price and quantity.

We note that the impact of competition could appear in price, quantity, or both. For example, if the biosimilar bid were used to create competition for the reference biologic but then the hospital never chose the biosimilar, market prices would be lower as a consequence of the tendering, but biosimilar sales would be zero. Likewise, a tendering process might

result in limited price competition by the reference biologic and therefore high market share for the biosimilar.

There is a previous literature that examines the impact of buying institutions on price discrimination in the pharmaceutical industry.[14] First, there is considerable price dispersion in what different countries pay for prescriptions drugs. This is likely partially due to income differences and willingness to pay. However, buying institutions matter also, as shown in Duggan and Scott Morton (2010).[15] There are two basic mechanisms. One is that in a bargaining game the outside options of both parties matters. If the buyer can set up institutions in its country to make the outside option of the pharmaceutical manufacturer worse, then it can obtain a better contract. Another mechanism is institutional design that causes the buyer to become more elastic. A monopoly seller's optimal price then declines in response. A system of list prices where all products are approved and the physician chooses does not make national demand elastic, whereas a competitive tender by the hospital-as-residual-claimant does.

4 Data

4.1 IMS data

We use data from IMS Health on revenues and quantities sold of all biologics in 23 countries, all European except for Australia. Table 1 tabulates the data by country. The years covered are 2007 to 2012 inclusive. The data arrive with a flag for reference type: brand or biosimilar. We carefully examined and cleaned the data and found no errors in the categorization of the product and very few other problems.[16] There are three molecules that have experienced biosimilar entry in Europe during the time period of our data: Epoetin, which stimulates

[14] Danzon, Patricia M., and Li-Wei Chao. "Cross-national price differences for pharmaceuticals: how large, and why?." Journal of health economics 19.2 (2000): 159-195.

[15] See also Price Discrimination in Input Markets, by Roman Inderst and Tommasso Valetti. RAND, 2009.

[16] Other researchers should be aware that IMS creates a price by dividing revenues by quantities, but then reports a rounded quantity. Re-creating price by dividing revenue by the rounded quantity results in large price outliers when quantities are small. It is possible to reconstruct the non-rounded quantity by dividing revenue by price again.

red blood cell production in the body, Filgrastim, which stimulates the bone marrow to produce blood cells (used after chemotherapy), and Somotropin, a human growth hormone. There are slightly different versions, or generations, of Epoetin on the market in Europe, Epoetin-Alpha, Epoetin-Lambda, and Epoetin-Zeta. We combine these into one molecule for our analysis. The drugs are also produced in different forms. For example, the number of milliliters of liquid in the syringe, or a liquid versus a powder. It is often the case that the biosimilar enters a national market with only one form while the incumbent reference product produces several forms. Treating each form as a separate product results in very little "entry" as a fraction of the number of markets. Instead we combine all forms sold by the same firm in the same country and year into one observation. We can do this very accurately because IMS provides a variable called "standard units" which converts each form type into common units.

We create a price variable for biosimilars as follows. We take the branded price in the first year of the data, 2007, or the year in which the brand first appears in the data, whichever is earlier. This becomes the benchmark branded price and is the denominator of our relative price variable in all future years. The price of biosimilars sold in that country (c) and year (t) is the numerator. There may be multiple manufacturers of biosimilars s, so we take a weighted average of their prices each year. For each of our three drugs in the sample:

$$P_{ct}^{relative} = \frac{\frac{\sum_s q_{sct} p_{sct}}{\sum_s q_{sct}}}{p_{bc_{2007}}} \tag{1}$$

Thus if one biosimilar enters at 80% of the branded price the relative price variable will be 0.80. If in the next year the brand matches the biosimilar price, our ratio will not return to one. This is desirable because both prices are lower than the initial brand price due to biosimilar entry. Because we define the denominator as the 2007 brand price, in this example the ratio of generic (2008) to brand (2007) will remain unchanged.

Our quantity variable is a measure of penetration of biosimilars. We sum biosimilar units in a country and year to form the numerator. The denominator is all units sold of the

molecule in that country year, both biosimilar and brand. Price is not used to weight the units sold. For each of our three drugs in the sample:

$$Q_{ct}^{share} = \frac{\sum_s q_{sct}}{\sum_s q_{sct} + q_{bct}} \tag{2}$$

Our analysis will be focused on these measures of biosimilar success. The empirical section of the paper will try to explain why biosimilars are or are not a significant fraction of consumption in the countries in our data, and whether biosimilar prices are lower than the branded molecule price prior to entry.

Summary statistics for our IMS dataset follow in Table X. There is steady entry by biosimilars across markets and drugs. Figure 7 shows the growth in total markets entered by biosimilars over time.

Prices are variable over time and across countries, even for the same product from the same manufacturer, but quantities are growing over time. Figure 5 plots market shares over time and Figure 6 plots relative prices over time. Relative prices of biosimilars also show considerable variation. Though the mean is below one, as we expected. There are a number of drug-country-year combinations where the biosimilar is much more expensive than the 2007 branded biologic. The average quantity sold in these observations is low, however.

4.2 Procurement of biosimilars in Europe

For each country in the sample we investigated the manner in which biologics and biosimilars are purchased. Recall that the EMA has approved these medications for all of the EU in terms of safety and efficacy. The variation across countries in consumption occurs because each one has a different process to determine reimbursement and encourage or discourage usage of the molecule and specific makers.

In every country there is a government agency that determines whether a new product will be included in the national health scheme and sets either a price or a reference group for it. (The Appendix lists the relevant agencies that approve new products and set prices in each of the countries in our dataset.) A typical process is as follows. The pharmaceutical

division of the health ministry negotiates with the manufacturer and agrees that the biosimilar will be added to the list of drugs for which providers will be reimbursed. The biosimilar's price is then determined, often through negotiation. For example, the health ministry and the manufacturer might agree that the biosimilar will be priced 20% below the price of the reference brand product. After the drug is available in the country, physicians prescribe it in in hospital, clinic, or outpatient settings and the government pays the bill.

Note that in the example above the taxpayer/government benefits if the biosimilar is used because it is 20% less expensive. However, there is no financial incentive to use the biosimilar borne by the hospital, clinic, or physician. In every case the government will pay the negotiated price; the biosimilar is cheaper but the benefit from using the biosimilar does not accrue to the decision maker in any significant way.

Recognizing this problem, recently some countries in Europe have devised procurement schemes to create price competition between the reference biologic and the biosimilar. Most typically this is done by empowering an agent in the system to seek competitive bids for the molecule. The agent retains the savings from carrying out a competitive tender. For example, in England each hospital has a budget and can procure biologics with a competitive tendering process. If the biosimilar bid is the lowest, then the hospital has an incentive to purchase the biosimilar instead of the reference product and use the saved resources for some other activity. A second example comes from Germany where the large insurance companies (sickness funds) are paid in a capitated fashion and therefore create and run drug formularies. These organizations negotiate for discounts and may choose the biosimilar to be the biologic on the formulary for everyone covered by their insurance. These types of financial incentives and procurement schemes are likely to push down the price of the biosimilar and increase its use.

A team of research assistants assembled documents and regulations from each country in our dataset. Research assistants and authors also conducted telephone interviews of local experts. Determining the nature of procurement was difficult for two reasons. First, it varies by drug because these drugs are distributed through different channels, e.g. hospital

versus ambulatory distribution. Secondly, the official regulations do not always deliver a complete picture and an interview is required to determine the true nature of the regulation. For example, hospitals in Ireland could procure biologics by competitive tendering, but until recently their incentive was to purchase the product with the highest list price. In that way, the absolute size of the discount was largest, and was retained by the hospital. Tendering designed this way has the perverse effect of encouraging the purchase of a high priced reference biologic. We therefore create two categories of "tendering," one standard, and one perverse. In other cases a hospital may be permitted to tender under the regulations, but it does not. Frequently biologics are "carved out" of standard healthcare regulations. Other pharmaceuticals may require a copayment if the patient purchases the brand rather than the generic. Because biosimilars officially are not generics, they are often exempted from this type of financial incentive scheme.

The procurement questions we used are as follows:

Procurement Incentives:

- NATL: a national agency procures bids for national demand. The winner of the auction or tendering process supplies all patients in the country, or all new patients in the country.
- INSR: an insurer has a budget (or is paid a fixed fee) to provide care and procures bids for biologics
- HOSP: a hospital has a budget to provide care and procures bids for biologics
- PHYS: national agency approves products at fixed prices. Physicians decide what product to use but have no financial incentive.

These four types of procurement policies as we have designed them are mutually exclusive and exhaustive. We also looked for other policies that might affect the pricing and utilization of biosimilars in a country. These factors we consolidated into the following

questions. Again, the answers are sometimes different across drugs due to differences in cost or distribution channel.

Other variables:

- Can biosimilars be substituted for the reference biologic by the pharmacist? (rare)
- Does the patient pay a copayment that is higher for the more expensive drugs?
- Does the country have a quota for biosimilar use?
- Does the national health agency conduct physician education on biosimilars?
- Does the national health agency conduct patient/consumer education about biosimilars?
- Has a local pharmaceutical or health agency conducted a study or review of the performance of biosimilars in the specific country?

Another complication with the procurement data is that countries may alter their policies part way through our sample. When we find evidence of a policy change, we note the date, and include that in our dataset. For example, if competitive tendering is adopted in 2010, we would expect to see a higher utilization of biosimilars in 2010 and onwards than in previous years.

The results of this survey are shown in Table 3. We see considerable variation in procurement policies. Many countries do not have competitive tendering, co-payments, or physician education. Entry increases strongly over time. We note that overall national fiscal health does not seem to be strongly related to the existence of competitive tendering. To the extent that there is a correlation, it is that more fiscally healthy countries are more likely to have effective procurement policies. For example, Germany is exemplary. However, while Greece has no policies to promote biosimilars and Spain has very few, Sweden also does very little. We view the lack of correlation between fiscal health and prudent purchasing as an interesting example of the difficulties of getting financial incentives to trickle down within a

bureaucracy. While the health minister may be very concerned about the budget, suitably incentivizing the purchasing manager for biologics at a hospital is not straightforward.

5 Graphs and Estimation

The data are usefully displayed visually, as much of the story is clear by inspection. Quantities purchased of biosimilars are trending up across almost all countries. Prices are stable or trending down. There are a few cases of very high biosimilar prices, relative to the brand. We do not have an explanation of why we are seeing these high prices. It is not measurement error as far as we know. We note that relative prices above 1.5 occur in countries that purchase small amounts.

The first set of tables we show are regression of relative biosimilar price or biosimilar quantity share on a series of fixed effects: drug, country, and year. We also include a time trend rather than year fixed effects as that fits the data well (the r-squared declines from 0.54 to 0.53) and saves on degrees of freedom. We also report an anova that interacts drug and country fixed effects to determine if there is something idiosyncratic about demand for each drug in each country. We find that marginal R-squared goes up considerably to 0.68.

The second set of tables uses our procurement data in place of country fixed effects. We create an indicator variable for a drug-country-year that has any form of competitive tendering. We have indicator variables for different types of tendering, as described above, to see if they operate differently. The other variables we include are the financial incentive of the patient, the existence of quotas, and physician education concerning biosimilars. The results are presented in table X.

One can immediately see that there is a strong trend for biosimilar penetration to rise over time at about 9% per year. There are significant differences across drugs and across countries. Tendering increases penetration, as does physician education. The tendering result appears to come from the insurance tendering variable. Hospital tendering has the wrong sign in the quantity regressions. Our suspicion is that many countries *allow* for competitive hospital tendering in their regulations but not many of them actually carry it

out. So we are not able to pick up the correct impact of the practice due to measurement error.

The price regressions show slightly different patterns. The trend in price is not downward, though on average biosimilars cost less than brands. Tendering and patient co-pays have negative signs but are significant at only the 10% level. National tendering and physician education seem to drive down prices while hospital tendering, once again, has the wrong sign.

It is possible, for example, that countries that physician education proxies for the countries that carry out hospital tendering, rather than being an effect due to the education. We plan to explore the interactions among these variables in the next iteration of the paper. We will also have procurement data that vary by year as we improve our measures, and to the extent that countries vary their policies in our time window, this will add power to our analysis.

6 Conclusions and Implications for the United States

The empirical evidence from Europe can help United States policy makers think about the most cost-effective way to procure biologic drugs in an environment where biosimilars are available. These biosimilars can generate cost savings, as we see in the European data.

How do US payor institutions need to be modified in order to create the price competition we have seen under Hatch-Waxman in small molecule drugs? For example, biotech drugs are generally physician-administered, rather than sold at the pharmacy, and are often covered under a medical benefit, not a pharmacy benefit. Physician administered drugs are not included in Medicare Part D, but in Medicare part B, which is the part of Medicare that covers doctor visits. Physician-administered drugs (PADs) are not typically managed by a pharmacy benefits manager, nor are they subject to the same sort of formularies that allow a buyer to move market share in response to price. Moreover, PADs are normally recorded by the physicians office under a J-code. If there is more than one drug that treats a condition, they often share a J-code. Thus the final payor/insurer has no way to know

which product the physician bought and therefore with which manufacturer to negotiate for a lower price.

The logistics of biologic use in the United States mean it will be very difficult for the insurer to bargain for a discount in return for instructing physicians to use the drug rather than a competitor. Policy makers in the US may need to analyze their buying institutions to figure out how to create price competition among substitute biologic drugs.

Tables and Figures

Table 1: Data by country

	x	x	x
x	x	x	x

Table 2: IMS summary statistics

	x	x	x
x	x	x	x

Table 3: Procurement incentives by market*

	Epoetin	Somatropin	Filgrastim
Physican Ed.	13.77%	9.42%	13.77%
Patient Co-Pay	52.17%	47.83%	47.83%
Tender	52.90%	34.78%	61.59%
Hosp. Tender	21.74%	8.70%	4.35%
Insur. Tender	8.70%	8.70%	4.35%

Percent of sample with given incentive/policy
N = 138 country-market-years

Table 4: Predicting biosimilar share

Outcome = biosimilar share of total unit sales				
country==Austria	0.24***	0.24***		
	(0.05)	(0.05)		
country==Belgium	0.01	0.01		
	(0.06)	(0.06)		
country==Bulgaria	0.17***	0.17***		
	(0.06)	(0.07)		
country==Denmark	0.12*	0.12*		
	(0.06)	(0.06)		
country==Finland	0.26***	0.26***		
	(0.07)	(0.07)		
country==France	0.14**	0.14**		
	(0.05)	(0.05)		
country==Germany	0.53***	0.53***		
	(0.09)	(0.09)		
country==Greece	0.28***	0.27***		
	(0.07)	(0.06)		
country==Hungary	0.10*	0.10*		
	(0.05)	(0.05)		
country==Ireland	0.08	0.08		
	(0.06)	(0.06)		
country==Italy	0.08	0.08		
	(0.05)	(0.05)		
country==Latvia	0.22**	0.22**		
	(0.09)	(0.09)		
country==Lithuania	0.15***	0.15***		
	(0.05)	(0.05)		
country==Norway	0.56***	0.56***		
	(0.11)	(0.11)		
country==Poland	0.38***	0.38***		
	(0.08)	(0.08)		
country==Portugal	0.12	0.12		
	(0.07)	(0.07)		
country==Romania	0.31***	0.31***		
	(0.06)	(0.06)		
country==Slovakia	0.24***	0.24***		
	(0.07)	(0.07)		
country==Slovenia	0.10*	0.10*		
	(0.05)	(0.05)		
country==Spain	0.10**	0.10**		
	(0.05)	(0.05)		
country==Sweden	0.37***	0.37***		
	(0.09)	(0.09)		
country==UK	0.15**	0.15**		
	(0.07)	(0.07)		
trend		0.09***	0.09***	0.09***
		(0.01)	(0.01)	(0.01)
Any tender process			0.07**	
			(0.03)	
Patient co-pay			-0.03	-0.04
			(0.03)	(0.03)
Quota			0.01	-0.02
			(0.04)	(0.03)
Physician education			0.07*	0.05
			(0.04)	(0.04)
National tender				0.00
				(0.02)
Hospital tender				-0.06*
				(0.03)
Insurance tender				0.17***
				(0.06)
Perverse incentives				-0.03
				(0.09)
N	404	404	404	404
R^2	0.54	0.54	0.36	0.39

* p<0.10, ** p<0.05, *** p<0.01
All models include year and molecule fixed effects

Table 5: Predicting biosimilar relative prices

Outcome = price of biosimilar relative to pre-entry brand				
country==Austria	-0.01			
	(0.18)			
country==Belgium	-0.35			
	(0.25)			
country==Bulgaria	-0.15			
	(0.20)			
country==Denmark	0.21			
	(0.24)			
country==Finland	0.22			
	(0.28)			
country==France	-0.14			
	(0.20)			
country==Germany	-0.14			
	(0.22)			
country==Greece	0.42			
	(0.26)			
country==Hungary	0.27			
	(0.28)			
country==Ireland	-0.27			
	(0.23)			
country==Italy	0.41*			
	(0.23)			
country==Latvia	-0.44**			
	(0.21)			
country==Lithuania	0.23			
	(0.24)			
country==Norway	0.88***			
	(0.22)			
country==Poland	0.03			
	(0.29)			
country==Portugal	1.40*			
	(0.74)			
country==Romania	0.18			
	(0.21)			
country==Slovakia	0.43			
	(0.33)			
country==Slovenia	0.02			
	(0.21)			
country==Spain	1.11**			
	(0.47)			
country==Sweden	0.30			
	(0.21)			
country==UK	-0.03			
	(0.19)			
Any tender process		-0.17*		
		(0.10)		
Patient co-pay		-0.02	0.08	0.08
		(0.11)	(0.11)	(0.11)
National tender			-0.18**	-0.21**
			(0.07)	(0.08)
Hospital tender			0.26**	0.23**
			(0.10)	(0.10)
Insurance tender			0.19	0.09
			(0.21)	(0.22)
Quota			-0.05	-0.02
			(0.13)	(0.13)
Physician education			-0.25**	-0.28***
			(0.10)	(0.11)
Publiced				0.11
				(0.12)
N	237	237	237	237
R^2	0.33	0.11	0.20	0.20

* p<0.10, ** p<0.05, *** p<0.01
All models include year and molecule fixed effects

Figure 1: Epoetin Biosimilar Market Penetration

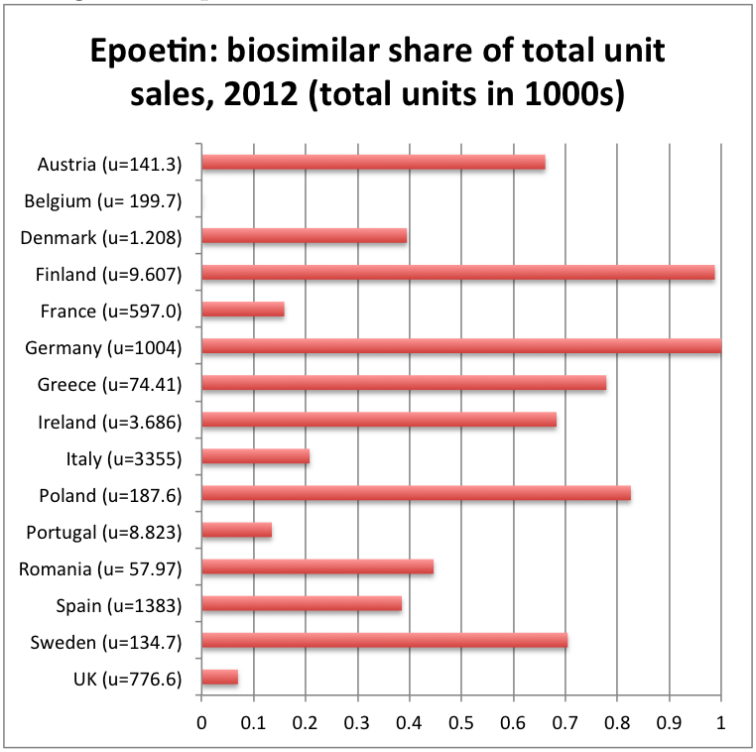

Figure 2: Somatropin Biosimilar Market Penetration

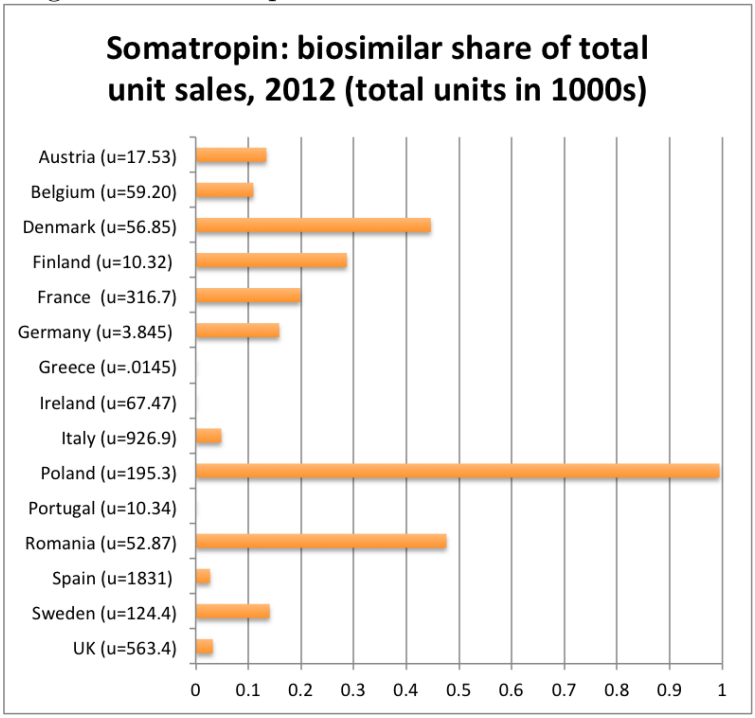

Figure 3: Filgrastim Biosimilar Market Penetration

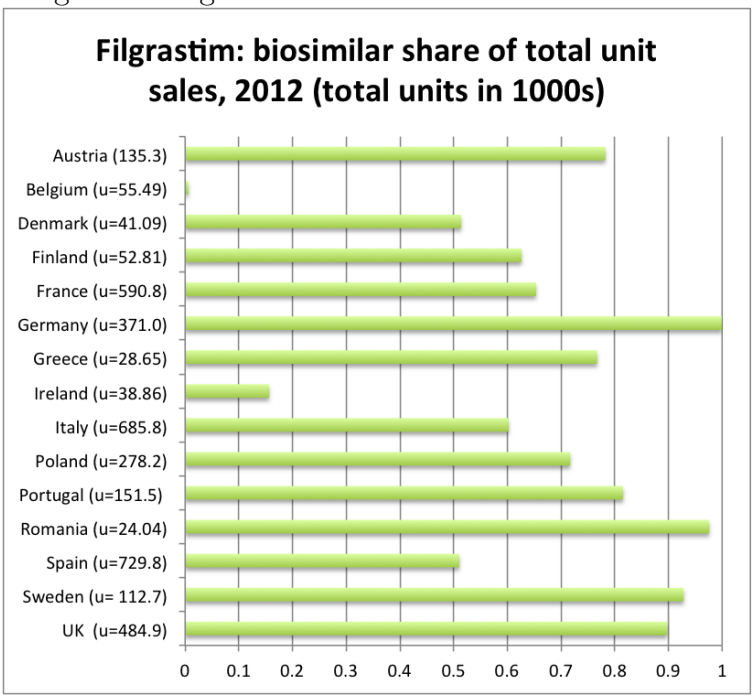

Figure 4: Comparing Biosimilar Market Penetration

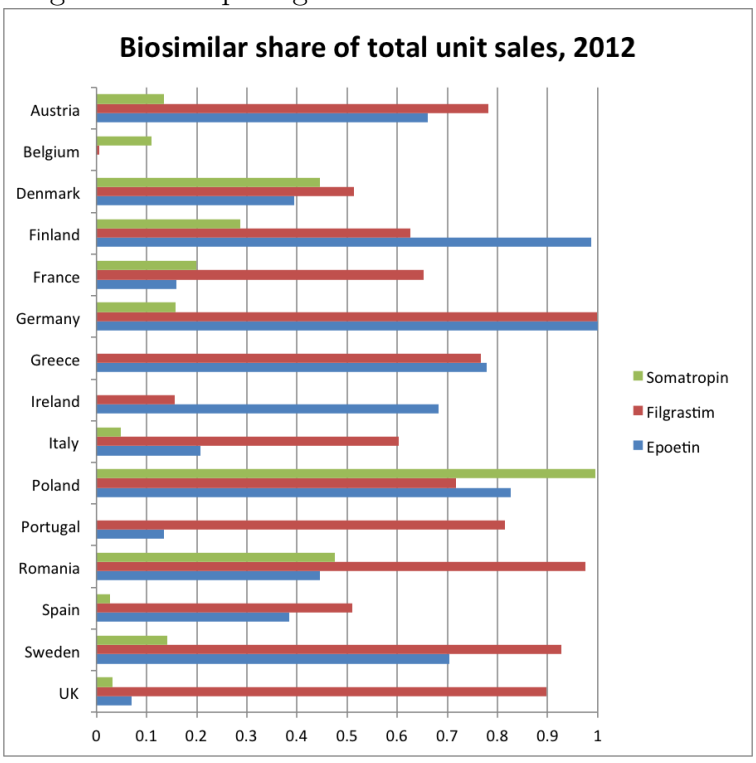

Figure 5: Market shares in the 10 largest markets

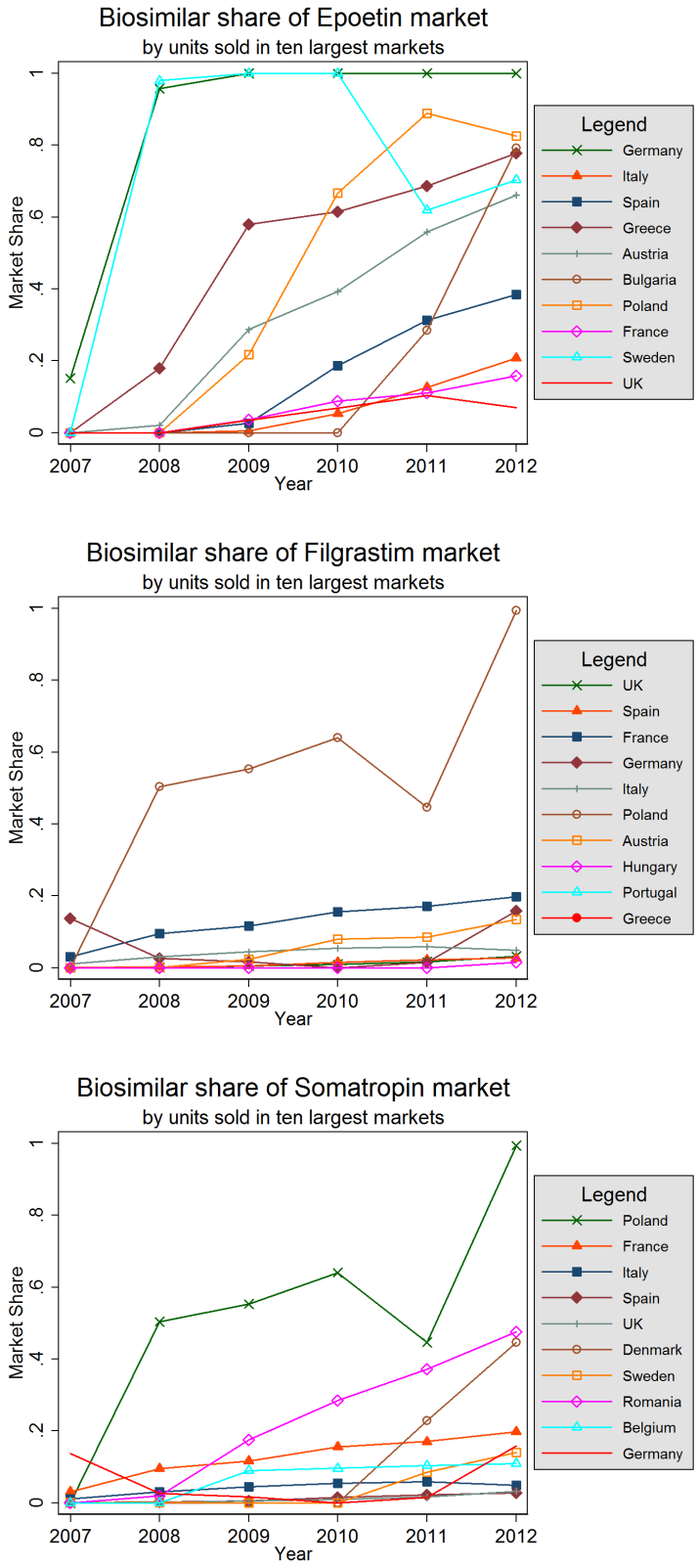

Figure 6: Relative prices (biosimilar price/pre-entry brand price) in the 10 largest markets

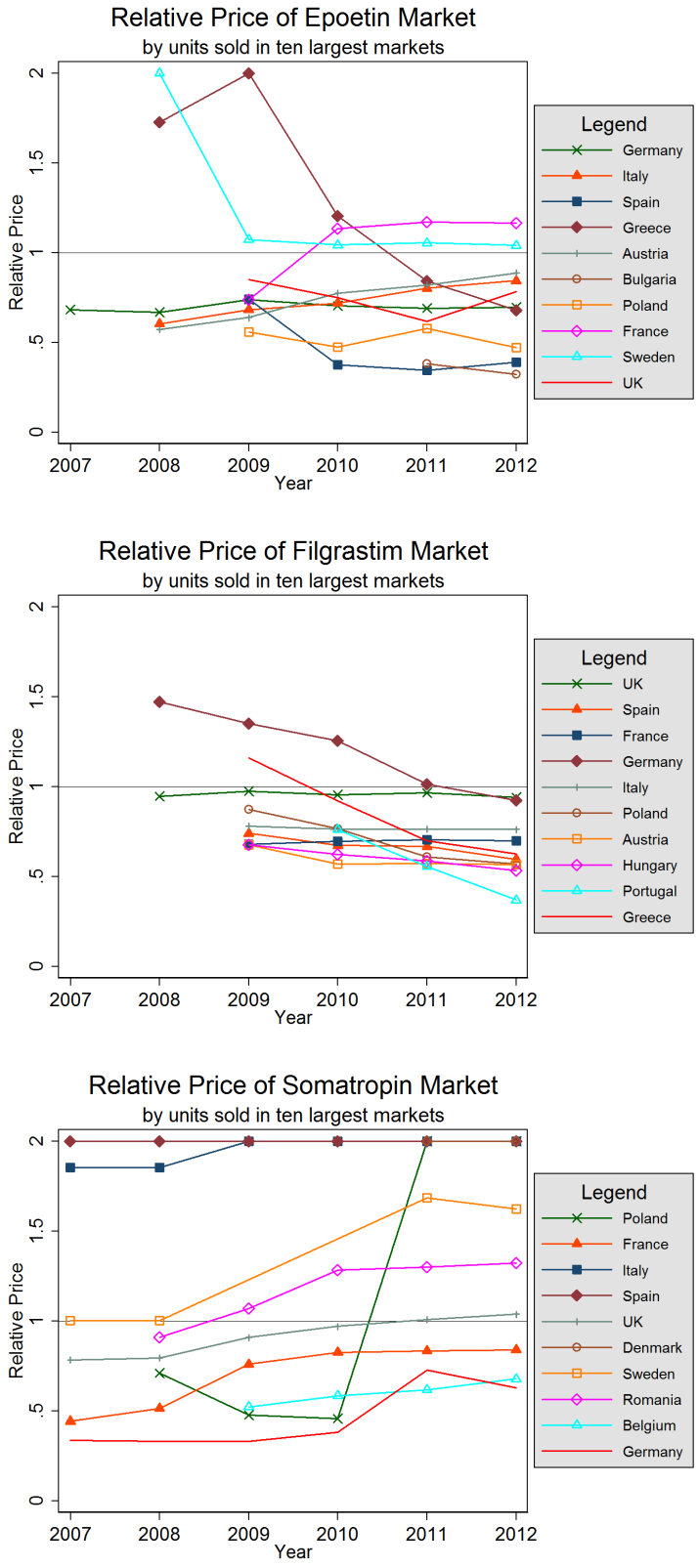

Figure 7: Entry in full sample