ONLINE APPENDIX to the paper

The Impact of the Entry of Biosimilars: Evidence from Europe

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Appendix A: Biosimilars in Australia and the United States

AUSTRALIA

Australia also has a regulatory pathway for biosimilar entry, and data from Australia are included in many of the analyses in this paper. 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 with the EMA, the TGA defines a biosimilar or similar biological medicinal product (SBMP[1]) 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.[2]

The Australian data requirements for the approval of biosimilars are based almost entirely on those outlined in EMA 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.[3] A full list of EU guidelines that have been adopted by the TGA for the approval of biosimilars can be found below,[4] but for all intents and purposes, policies and standards that govern the

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[1] 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.

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

[3] 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.

[4] Additional cites: 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)

approval of biosimilars in Australia are the same as those employed in the European Union and EMA decisions are adopted directly. Hence we include Australia in our empirical work.[5]

THE UNITED STATES

At present, most biologic therapies available in the United States 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 such as human growth hormone (hGH), insulin, and conjugated estrogens, which were approved as original 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 FDA.[6] Biologics are regulated by the Center for Biologics Evaluation and Research (CBER), while small molecule drugs are regulated by the Center for Drug Evaluation and Research (CDER).

In April of 2015, the FDA released final regulatory guidance on several, but not all aspects of the biosimilar approval process. The three final guidance documents issued address 1) "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product"; 2) "Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product"; and 3) "Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009."[7,8,9] The first of these documents, which is the most important of the three "is intended to assist sponsors in demonstrating that a proposed therapeutic protein product…is biosimilar to a reference product for purposes of the submission of a marketing application" (FDA, 2015). Importantly, the FDA has not yet released regulatory guidance to clarify the type and level of evidence required for interchangeability of biosimilars and reference biologics, which the FDA will release in a future guidance document. The FDA approved the first biosimilar application in March

[5] However all empirical results presented below are robust to excluding Australia from the sample.
[6] Biologics have 12 years of data exclusivity in the US, compared to 5 for small molecules.
[7] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf
[8] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf
[9] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf

2015, Sandoz's Zarxio (Filgrastim),[10] and three subsequent biosimilars (not yet launched at the time of writing) in 2016. Zarxio was marketed beginning in March 2015 at a launch price 15% below the reference biologic Neupogen.

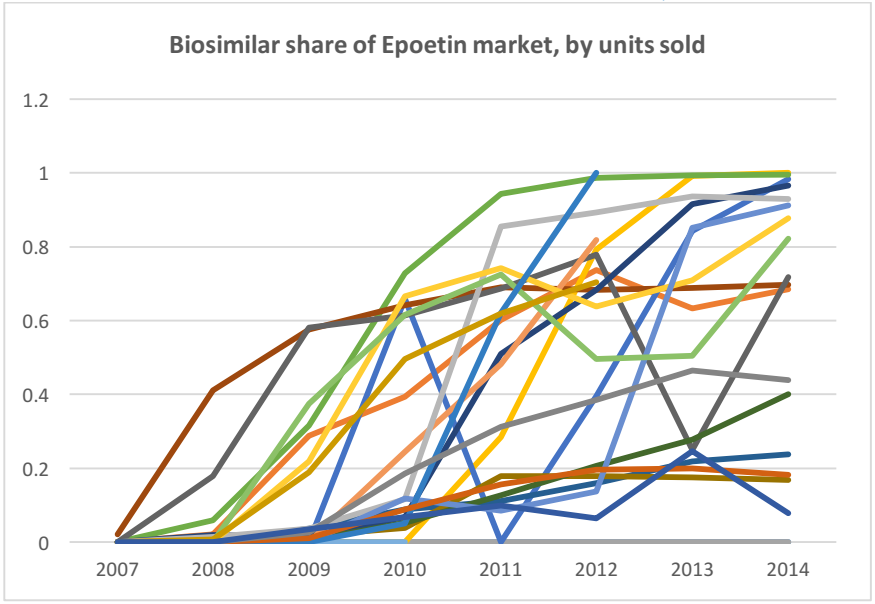
On February 4 of 2016, the Director of the Center for Drug Evaluation and Research (CDER) testified that "59 proposed biosimilar products to 18 different reference products were enrolled in the Biosimilar Product Development Program."[11] Enrolling in this program appears to both indicate interest in launching a product and also allows the applicant to meet with CDER, which Dr. Woodcock testified was happening with great frequency. She also said that as of December 31st 2015 five companies had publicly announced eight biosimilar applications. At the time of writing, only four biosimilar products[12] had been approved by the FDA and only one of those, Sandoz's Zarxio, had been launched.

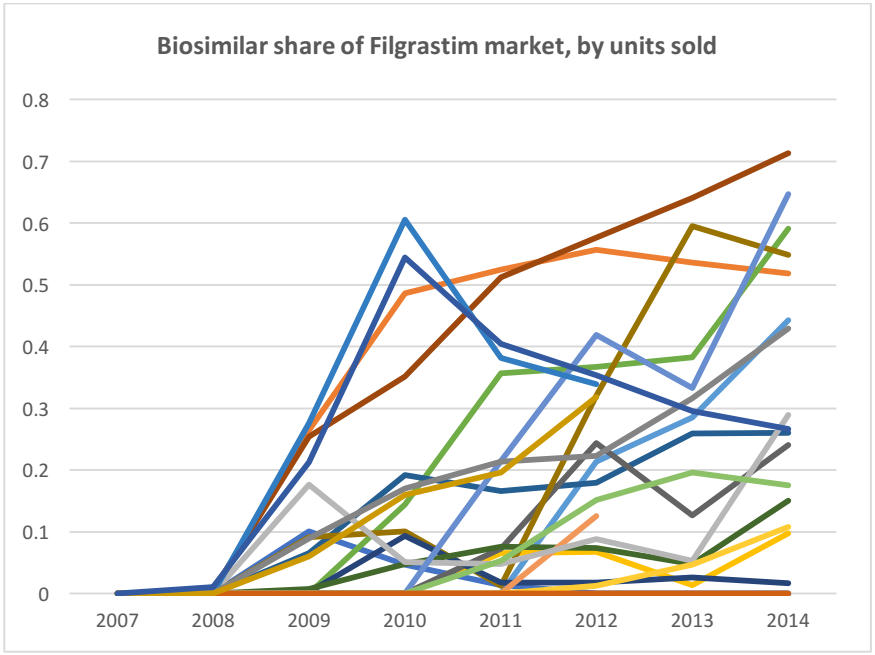
[10] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm
[11] Testimony by Dr. Woodcock before the House Committee on Energy and Commerce, subcommittee on Health, February 4, 2016.
[12] The four FDA-approved biosimilars as of January, 2017 were: 1) Zarxio, biosimilar to Neupogen, approved in March, 2015; 2) Inectra, biosimilar to Remicade, approved in April, 2016; 3) Erlezi, biosimilar to Enbrel, approved in August, 2016; and 4) Amjevita biosimilar to Humira, approved in September, 2016.

Appendix B: Supplementary Figures

Figure I. Biosimilar share of total domestic Epoetin/Filgrastim & Somatropin market (standard units) by country, 2007-2014

***** Fraction of total standard units that are biosimilar, conditional on biosimilar units > .001 of total units





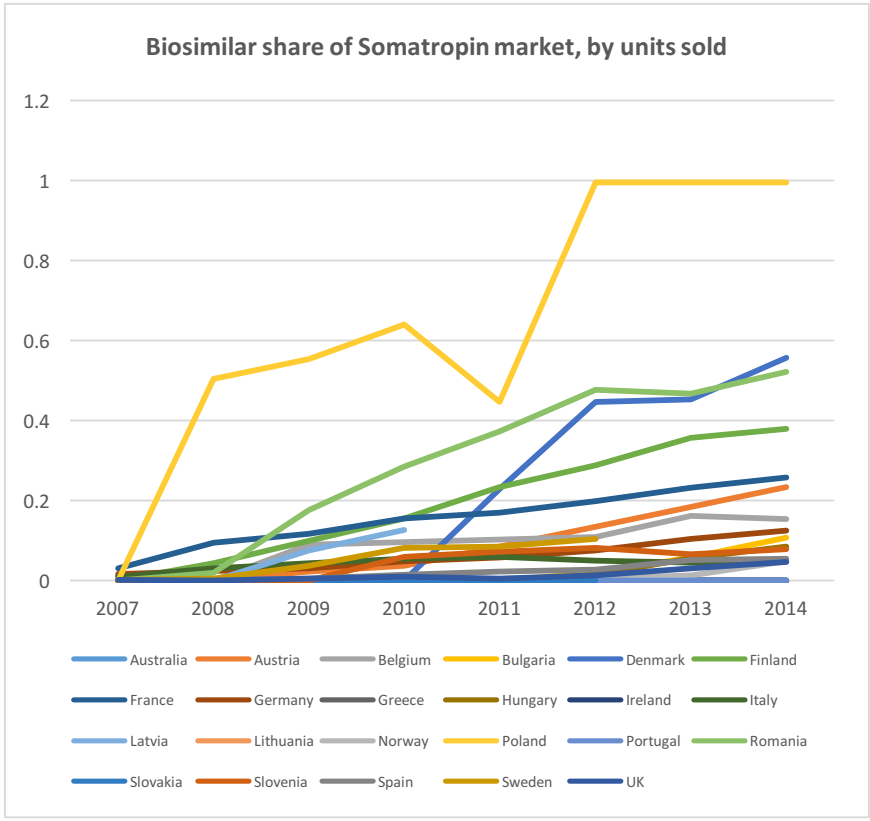
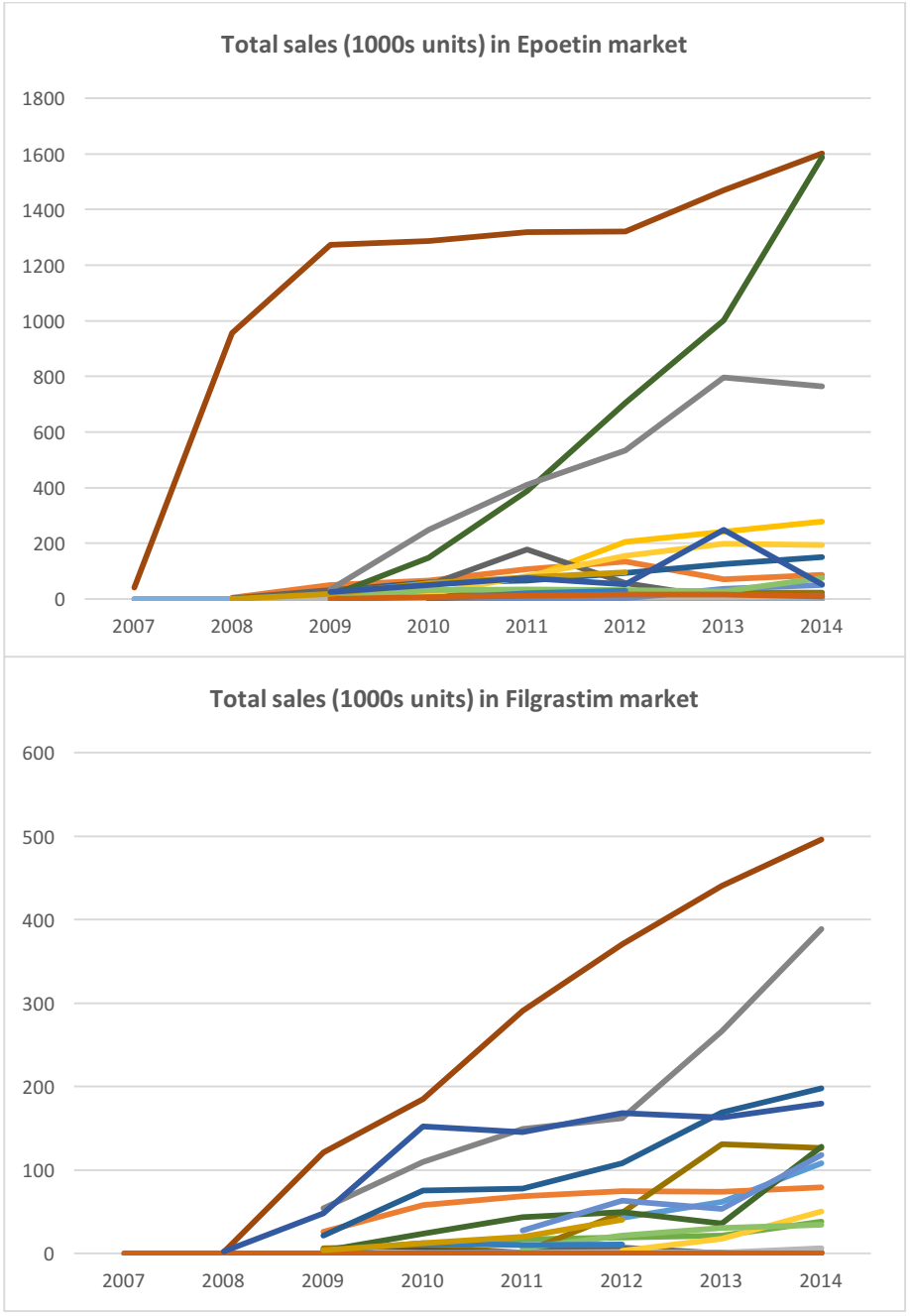


Figure II. Total sales in domestic Epoetin/Filgrastim/Somatropin markets (1000s units), 2007-2014

* Total biosimilar sales, conditional on biosimilar units > .001 of total units



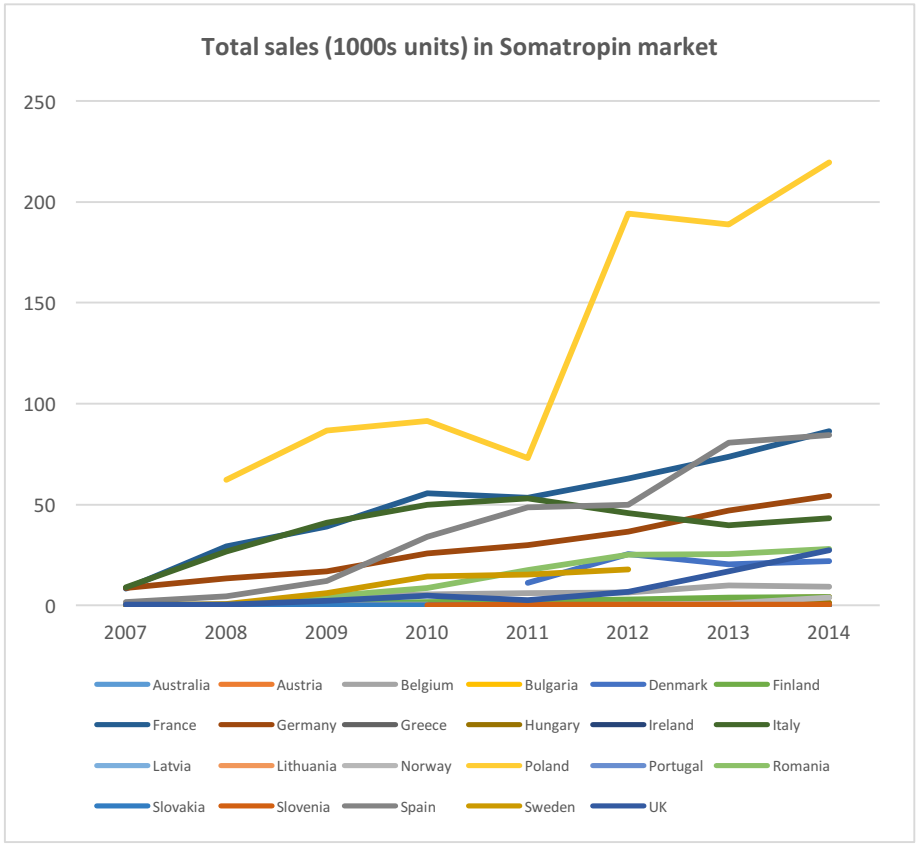
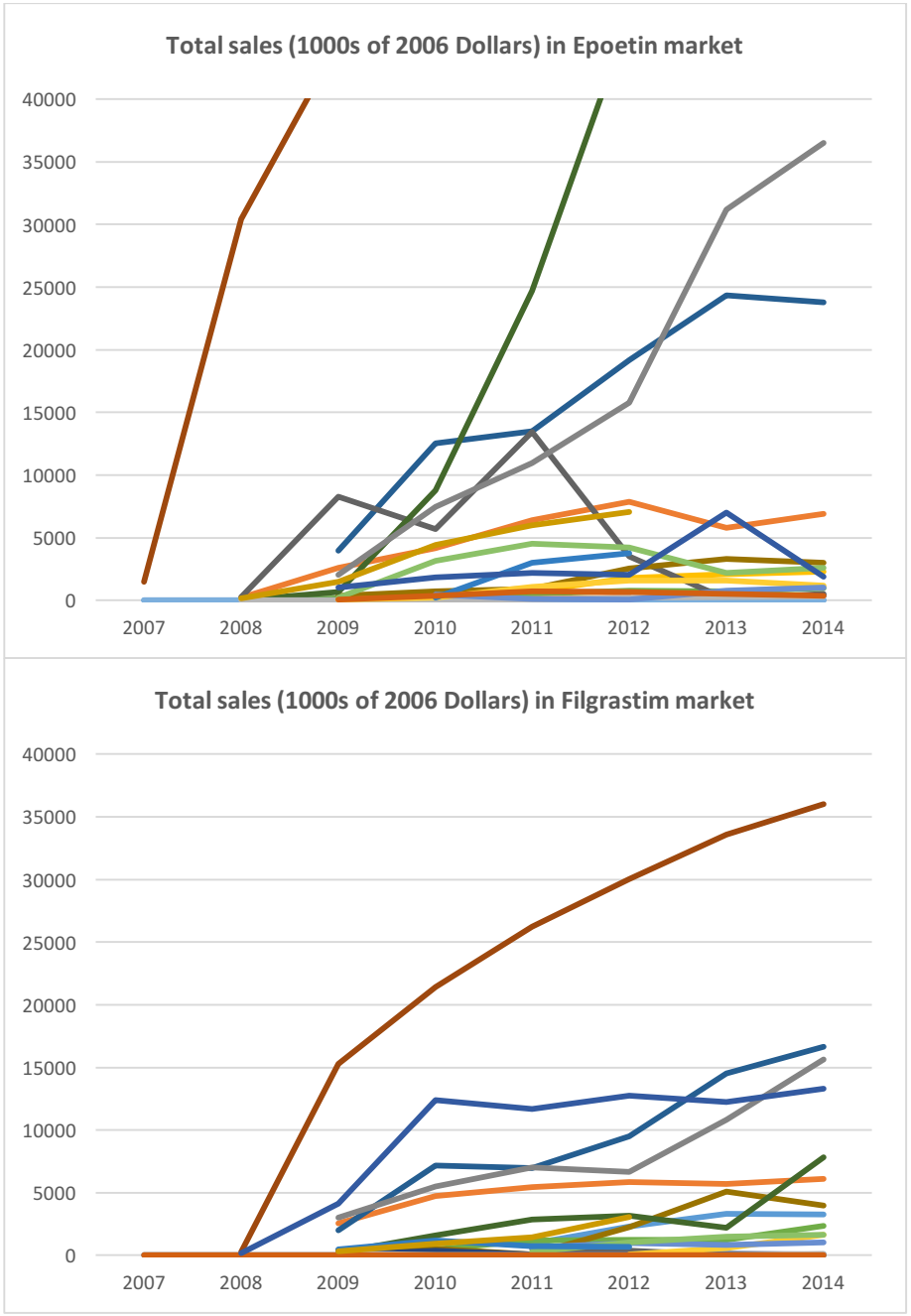


Figure III. Total sales in domestic Epoetin/Filgrastim/Somatropin markets (1000s 2006 dollars), 2007-2014

***** Total biosimilar sales, conditional on biosimilar units > .001 of total units



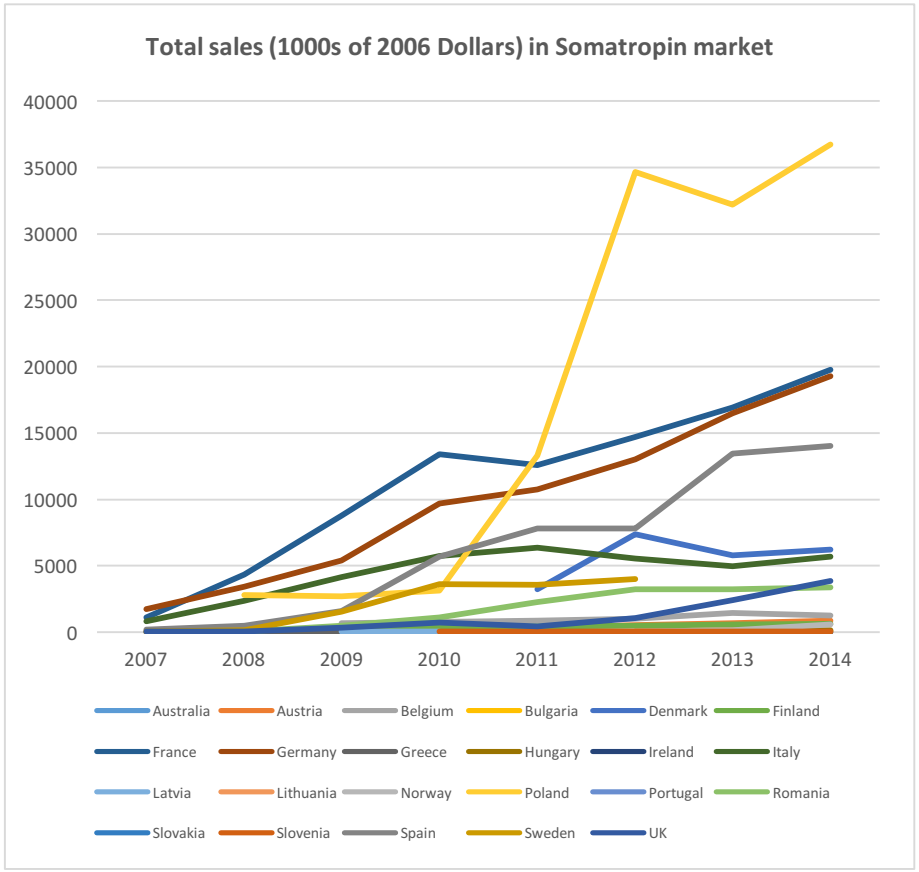
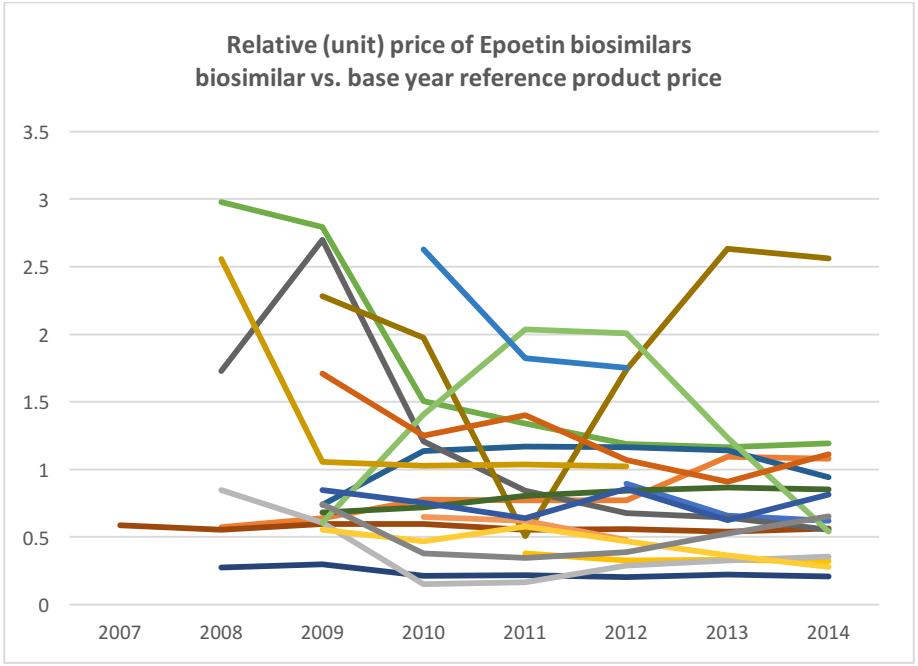
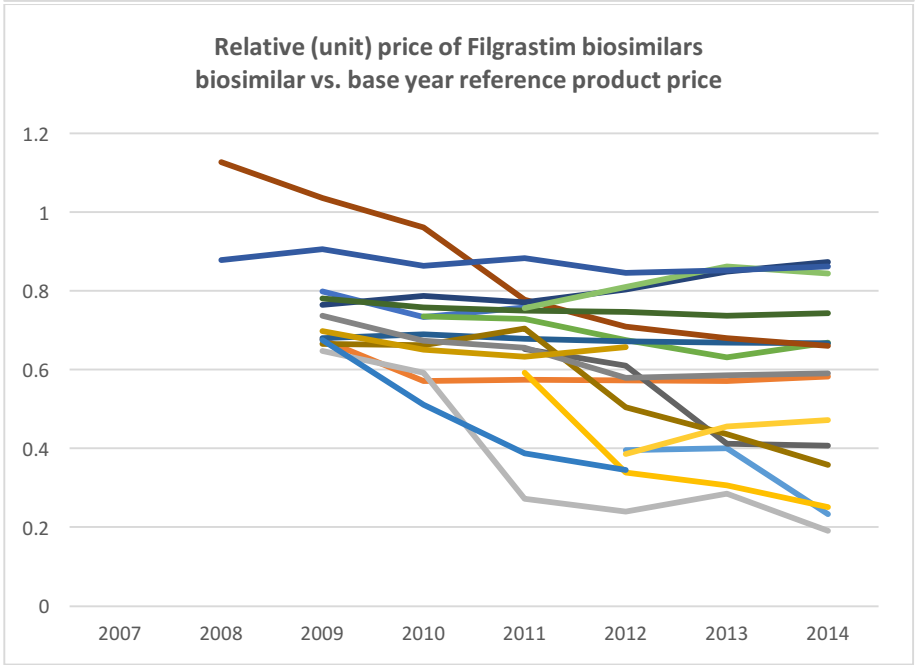


Figure IV. Relative prices: biosimilar vs. base year reference product price, Epoetin/Filgrastim/Somatropin, 2007-2014
***** Relative prices, conditional on biosimilar units > .001 of total units





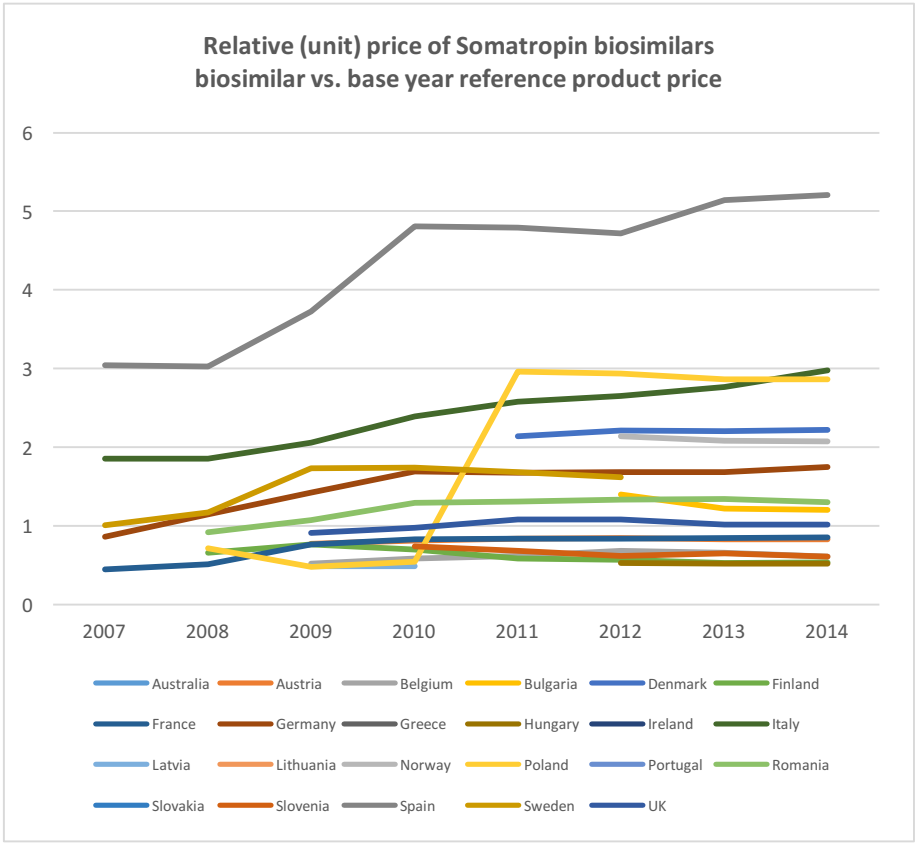
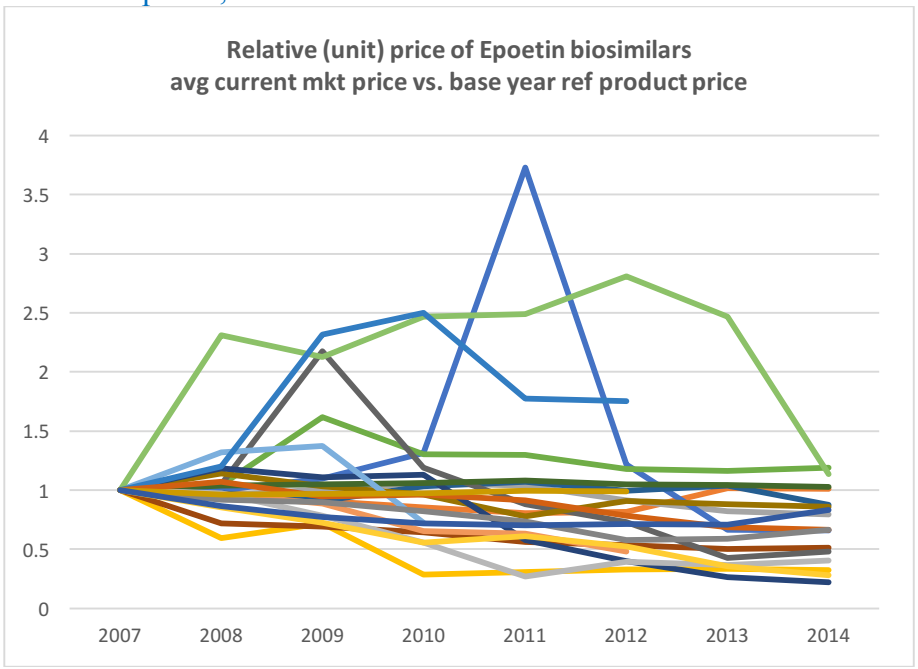
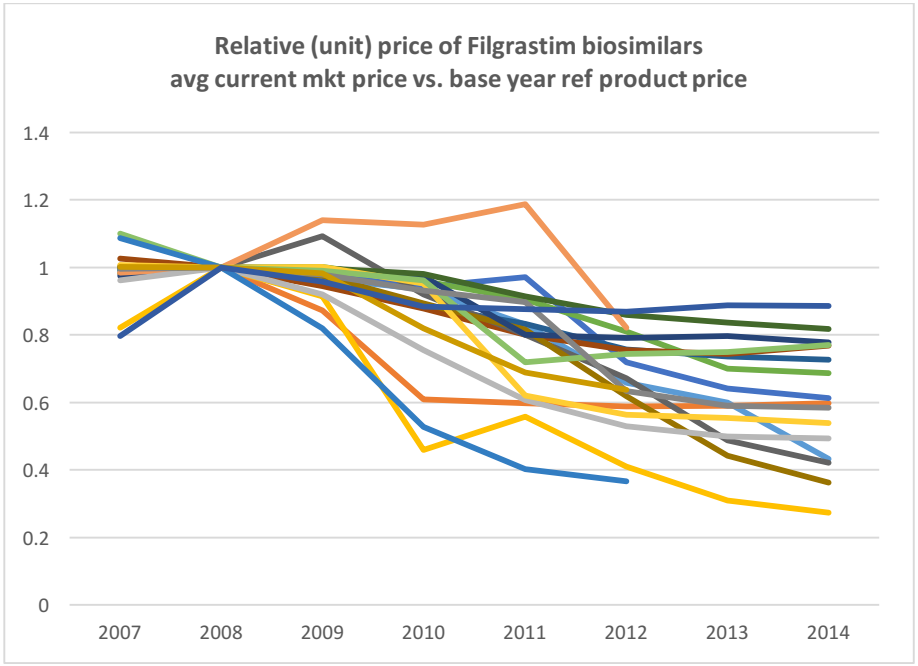
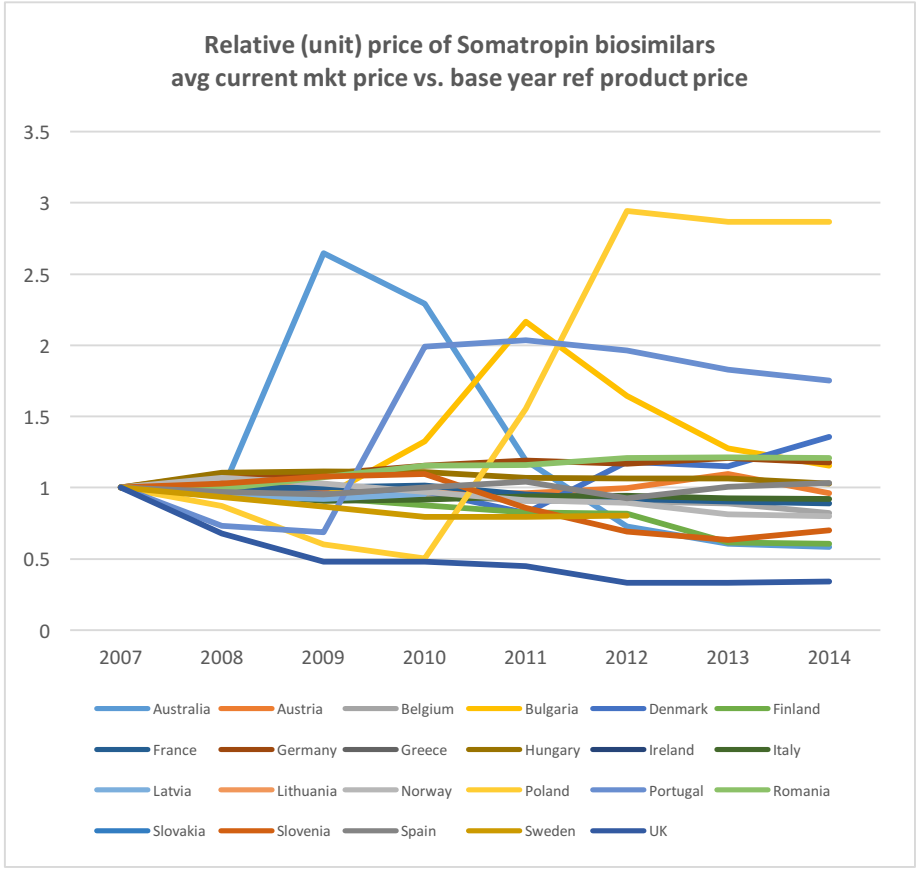


Figure V. Relative prices: average market price in current year vs. base year ref product price, Epoetin/Filgrastim/Somatropin, 2007-2014
***** Relative prices, conditional on biosimilar units > .001 of total units







Appendix C: Supplementary Tables

Table I. Legal requirements for a new biosimilar application to the EMA

The legal 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.[13]
- 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)
- 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

[13] 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.

Table II. List of sample countries with first year of biosimilar entry* in each market, 2007-2014

	Epoetin	Filgrastim	Somatropin
First EMA Approval	2007	2008	2006
Australia		2012	2007
Austria	2008	2009	2009
Belgium			2009
Bulgaria	2011	2011	2012
Denmark	2010	2009	2011
Finland	2008	2010	2008
France	2009	2009	2007
Germany	2007	2008	2007
Greece	2008	2011	
Hungary	2009	2009	2012
Ireland	2008	2009	
Italy	2009	2009	2007
Latvia			2009
Lithuania	2010	2012	
Norway	2008	2009	2012
Poland	2009	2012	2008
Portugal	2010	2011	
Romania	2009	2011	2008
Slovakia	2010	2009	
Slovenia	2009		2010
Spain	2009	2009	2007
Sweden	2008	2009	2007
UK	2009	2008	2007

*conditional on biosimilar units > .001 of total domestic units sold

Table III. List of individuals/organizations that assisted with policy survey

Andreja Jerina, The Directorate for Health, Sector for the development of health care, Slovenian Health Ministry, Slovenia

Carlos Lens, Pharmacy Deputy Director in the Ministry of Health, Social Services and Equality (MSSSI), Spain

Claire Biot, Director at Agence Générale des Equipements et Produits de Santé (AGEPS) AP-HP, France

Dr Maria Skouroliakou, Assistant Professor of Enteral and Parenteral Nutrition, School of Health Science & Education, Greece

Dr. Helder Mota Filipe, Associate Professor of Pharmacology and Therapeutics and Vice-President of Executive Board, INFARMED (National Authority of Medicines and Health Products, IP Portugal), Portugal

Dr. Fernando de Mora, Universitat Autònoma de Barcelona, Spain

Gustaf Befrits, Administrator in Pharma department of Stockholm County Council, Sweden

Hannes Enlund, FIMEA (Finnish Medicines Agency), Finland

Helga Festoy, Norwegian Medicines Agency, Norway

Italian Medicines Agency, Italy

Jens Ersboll, Danish Medicines Agency, Denmark

Karen Binnekamp, Pricing area of Department of Health, administer pharmaceutical benefit scheme (PBS), Australia

Maria Isabel Farfan, Expert economist, Belgium

Matthias Diesel, Head of Market Access, Pro Generika, Germany

Ministry of Health, Poland

Monika Lainczova, Manager of Drug Policy Deparment, Dovera Health Insurance Company, Slovakia

National Agency, Denmark

Pablo Serrano, Federal Association of the Pharmaceutical Industry BPI (Bundesverband der Pharmazeutischen Industrie e.V.), Germany

Roger Purcell, National Health Service, UK

Sabine Vogler, Gesundheit Österreich GmbH, Austria

Sandoz, Slovenia

Stanislav Primozic, Deputy Director of JAZMP, Slovenia

VFA Bio, Germany

Table IV. Chow Tests for sub-sample analyses

The Chow tests below show statistically significant differences between the slopes (coefficients) of the different groups (drug classes) to support interpreting coefficients from individual product class sub-samples.

	Columns 1-4		Columns 5-7	
	F/Chi Test statistic	p-value	F/Chi Test statistic	p-value
Table 5	118.66	0.0000	345.41	0.0000
Table 6	17.74	0.0000	178.98	0.0000
Table 7	9.87	0.0000	5.75	0.0001
Table 8	5.97	0.0001	n/a	n/a