ONLINE APPENDIX to the paper

*The Impact of the Entry of Biosimilars: Evidence from Europe*

Fiona M. Scott Morton, Ariel Dora Stern, and Scott Stern
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 (SBMP1) 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.

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.\textsuperscript{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.\textsuperscript{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.”\textsuperscript{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

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\textsuperscript{5} However all empirical results presented below are robust to excluding Australia from the sample.

\textsuperscript{6} Biologics have 12 years of data exclusivity in the US, compared to 5 for small molecules.

\textsuperscript{7} http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

\textsuperscript{8} http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf

2015, Sandoz’s Zarxio (Filgrastim), 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.” 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 had been approved by the FDA and only one of those, Sandoz’s Zarxio, had been launched.

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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.
- 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

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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

<table>
<thead>
<tr>
<th>First EMA Approval</th>
<th>Epoetin</th>
<th>Filgrastim</th>
<th>Somatropin</th>
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*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 Skouoliakou, 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 Department, 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.

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