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Biosimilars: Extrapolation for oncology

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ABSTRACT

A biosimilar is a biologic that is highly similar to a licensed biologic (the reference product) in terms of purity, safety and efficacy. If the reference product is licensed to treat multiple therapeutic indications, extrapolation of indications, i.e., approval of a biosimilar for use in an indication held by the reference product but not directly studied in a comparative clinical trial with the biosimilar, may be possible but has to be scientifically justified. Here, we describe the data required to establish biosimilarity and emphasize that indication extrapolation is based on scientific principles and known mechanism of action.

1. Introduction

Biologics are essential and widely used in cancer treatment as therapeutic agents (e.g., monoclonal antibodies [mAbs]) and as supportive care agents (e.g., growth factors). Because biologics are inherently variable complex molecules that are produced through manufacturing processes in living cells, they cannot be duplicated identically to a level typically possible for small-molecule drugs. Hence, the term "biosimilar" is used to describe a biologic that is highly similar to a licensed biologic product (the reference product) (European Medicines Agency, 2014; US Food and Drug Administration, 2015; World Health Organization, 2009). Because biosimilars are produced in living cells, differences may occur due to post-translational modifications (e.g., glycosylation) or altered higher order structure (protein folding and protein-protein interactions) that may affect the clinical outcome. Most of these

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differences can be detected with state-of-the-art analytical methods, but not all. Therefore, the approval of any biosimilar has to be based upon the overall assessment of biosimilarity to the reference product through robust analytical, non-clinical and clinical studies that demonstrate that the proposed biosimilar and the reference product are highly similar and there are no clinically meaningful differences between the two products in terms of purity, safety and efficacy (European Medicines Agency, 2014; US Food and Drug Administration, 2015; World Health Organization, 2009). Variability in post-translational modifications also exist between different batches of the reference product but because they do not alter the clinical profile they are acceptable by the regulatory bodies (Schiestl et al., 2011).

High-quality, safe, and effective biosimilars have the potential to increase access to biologic therapies worldwide and to reduce cancer care costs. Despite the stringent process outlined by several regulatory bodies around the world for the approval of biosimilars, some clinicians may hesitate to use biosimilars, particularly in therapeutic indications that have been licensed based on data extrapolation, i.e., approved for use in an indication held by the reference product but has not been directly studied in a comparative clinical trial with the biosimilar (Danese et al., 2014; Grabowski et al., 2015). These uncertainties may be based on a lack of familiarity with the scientific concepts underlying the development and approval of biosimilars. In this article, we describe the data required to establish biosimilarity and emphasize that indication extrapolation is based on true scientific principles and known mechanism of action. We discuss the regulatory guidelines for indication extrapolation and provide specific examples from biosimilars that are already in use in oncology, as well as biosimilars that are in development.

2. Regulatory requirements to demonstrate biosimilarity

The regulatory requirements for biosimilars approval are generally similar across guidelines of the European Medicines Agency (EMA), World Health Organization (WHO), and United States (US) Food and Drug Administration (FDA). Although there are minor differences among the agencies, all require extensive evidence to show that a biosimilar is highly similar to a reference product (European Medicines Agency, 2014; US Food and Drug Administration, 2015; World Health Organization, 2009). Biosimilarity approval is granted based on the "totality of evidence," i.e., a comprehensive comparison of the proposed biosimilar and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, clinical safety, and efficacy (European Medicines Agency, 2014; US Food and Drug Administration, 2015; World Health Organization, 2009). Unlike the approval process for originator biologics that relies heavily on clinical trials to demonstrate efficacy, safety, and immunogenicity, biosimilars are approved based on extensive analytical and nonclinical data and abridged clinical data; the objective of a biosimilar development program is to demonstrate there are no clinically meaningful differences based on totality of evidence, not to re-establish benefit. The data required to demonstrate biosimilarity are generated in a stepwise approach, starting with extensive structural and in vitro functional comparisons of the proposed biosimilar and the reference product followed by non-clinical in vivo animal studies and clinical studies (European Medicines Agency, 2014; US Food and Drug Administration, 2015; World Health Organization, 2009). Each step of the comparability exercise is used to determine the level of biosimilarity of the proposed biosimilar and the reference product and to address any residual uncertainty about biosimilarity. The structural and in vitro functional characterization of the proposed biosimilar and the reference product is the foundation of a biosimilar development program and consist of analyses of primary (i.e., amino acid sequence), secondary, tertiary, and quaternary structures, including aggregation, posttranslational modification (e.g., glycosylation, phosphorylation, and deamidation), intentional chemical modification (e.g., PEGylation), and biological activities (US Food and Drug Administration, 2015). The extent and nature of the non-clinical in vivo animal studies and clinical studies will depend on the evidence obtained with each previous step (European Medicines Agency, 2014; US Food and Drug Administration, 2015; World Health Organization, 2009). The clinical program should include a comparative study or studies assessing PK, PD (if feasible), and safety/immunogenicity. In some cases, these data are sufficient to support biosimilarity; for example, in the case of Filgrastim Hexal (Sandoz GmbH, Kundl, Austria) (European Medicines Agency, 2009a), the comparability of efficacy to the reference product filgrastim (Neupogen®, Thousand Oaks, CA) based on a PD study in healthy volunteers was considered acceptable by the committee for medicinal products for human use of the EMA (European Medicines Agency, 2009a). However, if there is a residual uncertainty about possible meaningful differences between the proposed biosimilar and the reference product, an additional comparative clinical efficacy, safety, and immunogenicity study or studies may be required (European Medicines Agency, 2014; US Food and Drug Administration, 2015; World Health Organization, 2009; Baer Ii et al., 2014). In evaluating biosimilarity of a proposed biosimilar to a reference product, regulatory agencies will consider the overall research and development program, from analytical through clinical trial data (European Medicines Agency, 2014; US Food and Drug Administration, 2015; World Health Organization, 2009). The type and extent of data required to demonstrate biosimilarity may vary and will be determined on a case-by-case basis (European Medicines Agency, 2014; US Food and Drug Administration, 2015; World Health Organization, 2009).

3. Extrapolation of efficacy and safety data from one indication to another

After similarity with the reference product has been convincingly demonstrated based on the totality of evidence and the product is designated a biosimilar product, it is considered similar to the reference product in terms of structure, function, PK, PD, efficacy, safety, and immunogenicity. If the reference product is licensed to treat multiple therapeutic indications, extrapolation of indications may be possible, but has to be scientifically justified. Extrapolation is the approval of a biosimilar for use in an indication held by the reference product, not directly studied in a comparative clinical trial with the biosimilar. The amount of scientific justification required to support the extrapolation of indications may differ across regulatory agencies (Table 1). For extrapolation to be considered by regulatory agencies such as the EMA, FDA, and WHO, biosimilarity to the reference product has to be demonstrated based on a comprehensive comparability exercise that includes efficacy and safety/immunogenicity in a key indication, and the clinically relevant mechanism of action and receptors involved in each indication has to be the same (Table 1) (European Medicines Agency, 2014; US Food and Drug Administration, 2015; World Health Organization, 2009). If the mechanisms of action or receptors involved are different, additional data (e.g., PD measures) may be required to justify extrapolation of indication (European Medicines Agency, 2014; World Health Organization, 2009).

Extrapolation is essential to the concept of biosimilarity. The EMA states, "The primary rationale for data extrapolation is to avoid unnecessary studies in the target population for ethical reasons,

Table 1
Comparison of regulatory guidelines for extrapolation of indications.

	European Medicines Agency (2014)	US Food and Drug Administration (2015)	World Health Organization (2009)
General	—Extrapolation could be acceptable with appropriate scientific justification	—Extrapolation should be based on sufficient scientific justification	—If extrapolation is intended, a detailed scientific discussion on the benefit/risk should be provided
	—Extrapolation should be considered in light of the totality of data from the biosimilar comparability testing	—Efficacy and safety tested in most sensitive indication to detect clinically meaningful differences in safety (including immunogenicity) and efficacy	—Efficacy and safety tested in most sensitive indication
	—The studied therapeutic indication should be sensitive for differences in all relevant aspects of safety/efficacy		—Non-inferiority study design may not support extrapolation, especially from low dose to higher dose
Mechanism of action	—The reference product interacts with several receptors —The reference product has more than one active site/intracellular signaling pathway	—Target/receptors involved for each relevant activity/function —Binding, dose/concentration response and pattern of molecular signaling pathway —Product structure and target/receptor interactions —Location and expression of the target/receptors	—The clinically relevant mechanism of action and/or receptors involved
Safety/efficacy	—Extrapolation of immunogenicity from the studied indication/route of administration to other uses require justification	—Pharmacokinetics and bio-distribution	—Sufficient characterization of safety and immunogenicity with no unique/new safety issues expected
	—Patient-related factors (co-medications, comorbidities, immunological status)	—Immunogenicity in different patient populations	—Immunogenicity should be evaluated in patients with the highest risk for immune response
	—Disease-related factors (e.g., lysis of tumor cells)	—Differences in expected toxicities	
		—Any factor that may affect safety or effectiveness	

for efficiency and to allocate resources to areas where studies are the most needed" (European Medicines Agency, 2013). Replicating the efficacy and safety data of the reference product is considered scientifically not essential and sometimes even unethical (Weise et al., 2012).

If a proposed biosimilar is truly highly similar to the reference product, it is expected that all aspects of its therapeutic effects, including efficacy, safety, and immunogenicity, would also be similar. This principle is already applied for small-molecule generics, for which demonstration of PK bioequivalence to the reference product is usually sufficient to conclude therapeutic equivalence. For biosimilars, extrapolation of indications is appropriate if there is sufficient scientific justification and based on the data from the entire development program. If extrapolation of clinical data is intended, the clinical study/studies should be conducted in a therapeutic indication that is sensitive enough to detect clinically meaningful differences between the proposed biosimilar and the reference product (European Medicines Agency, 2014; US Food and Drug Administration, 2015; World Health Organization, 2009). It should be noted that the clinical program is only one component of the comparability exercise and its goal is to confirm the similarity established by the structural and functional characterization and to address any residual uncertainty pertaining to biosimilarity.

4. Extrapolation of indication for approved biosimilars in oncology

Several biosimilars approved for cancer treatment have been granted approval for all indications held by the reference product based extrapolation of efficacy and safety data. The following cases illustrate the scientific data needed for demonstration of biosimilarity and extrapolation of indication.

4.1. Filgrastim

Filgrastim (Neupogen), a granulocyte-colony stimulating factor (G-CSF), is widely used in oncology to prevent chemotherapy-induced neutropenia (Amgen Inc., 1991). Filgrastim is also approved for treatment in patients with acute myeloid leukemia, severe chronic neutropenia, or undergoing bone marrow transplantation or peripheral blood progenitor cell collection and engraftment (Amgen Inc., 1991). Several biosimilars to filgrastim have been approved in the European Union (Biograstim®/Filgrastim ratiopharm/Ratiograstim®/TevaGrastim® [Teva LTD, Castleford, UK]; Zarzio® [Sandoz, Holzkirchen, Germany]; Nivestim® [Hospira, Lake Forest, IL]), and recently in the United States (Zarzio® [Sandoz]) for all indications of the reference product (Neupogen) (Gascon et al., 2013). The extrapolation of indications for all filgrastim biosimilars was justified based on (i) overall data from the comparability exercise that included head-to-head comparisons to the reference product using analytical methods showing similar molecular structure and in vitro function, PK studies showing similar exposure, and PD studies showing effect on absolute neutrophil and CD34+ cell counts in healthy volunteers, and efficacy and safety (including immunogenicity) studies in patients with cancer; and (ii) the single mechanism of action of filgrastim, i.e., binding to G-CSF receptor and mediating the same biological activity (stimulation of bone marrow cells) (Gascon, 2012). Although biosimilars to G-CSF were approved by EMA for all indications held by the reference product, due to insufficient long-term safety and efficacy data, some concerns about their use for peripheral blood stem cell mobilization in healthy donors have been raised by the World Marrow Donor Association and the European Bone Marrow Transplantation Association (Schmitt et al., 2014; Shaw et al., 2011). A recent pooled analysis of five post-approval studies (N = 1302) of the filgrastim biosimilar Zarzio demonstrated that severe or febrile neutropenia occurred within the range observed for the reference product and the safety profile was consistent with that of the reference product, including in healthy stem cell donors (Gascon et al., 2013; Schmitt et al., 2014). The extrapolation of indications for the filgrastim biosimilars was based on the totality of evidence that demonstrated high similarity between filgrastim biosimilars and the reference product in terms of quality, safety, and efficacy, and the single mechanism of action; this was further supported

by results from post-approval studies (Gascon et al., 2013; Schmitt et al., 2014).

4.2. Erythropoiesis-stimulating agents

Erythropoiesis-stimulating agents (ESAs), including epoetin alfa (Epogen® [Amgen]; Procrit®/Eprex® [Janssen, Raritan, NJ]), and darbepoetin alfa (Aranesp® [Amgen]), are approved for the treatment of anemia induced by chronic renal failure or cancer chemotherapy (Niederwieser and Schmitz, 2011). Two epoetin biosimilars have been approved in the European Union and those are marketed by different license holders: HX575 (Epoetin alfa Hexal® [Hexal]; Abseamed® [Medice, Iselohn, Germany]; Binocrit® [Sandoz]) and SB309 (Retacrit® [Hospira]; Silapo® [Stada, Bad Vilbel, Germany]) (Niederwieser and Schmitz, 2011). Biosimilarity for HX575 and SB309 was established based on the comparison exercise with Eprex as the reference product. Approval was granted for all indications of the reference product based on the data from the entire research and development program, and the similar mechanism of action of epoetin across all approved indications (European Medicines Agency, 2007a,b). For HX575, although the clinical study in cancer patients did not allow any conclusion on whether the efficacy of HX575 administrated subcutaneously (SC) was comparable to that of Eprex, extrapolation of data – for anemia in patients with chronic renal failure to cancer patients – was based on the entire comparability exercise between HX575 and Eprex (European Medicines Agency, 2007a). The data included demonstration of the comparable efficacy after intravenous (IV) administration in patients with chronic renal failure, the similar PK/PD profile after repeat-dose administration of SC HX575 and Eprex in healthy subjects, the similar PK/PD profile after IV administration of HX575 and Eprex in healthy subjects and the safety profiles (including immunogenicity) of HX575 and Eprex in cancer patients were comparable (European Medicines Agency, 2007a). For SB309, although a study comparing SC administration of SB309 and Eprex has not been conducted, SB309 was approved for SC administration in cancer patients based on the entire comparability exercise between SB309 and Eprex (European Medicines Agency, 2007b). The data included demonstration of the similar efficacy and PK/PD profile after IV administration in patients with renal failure, the similar PK profile after SC administration that may suggest similar efficacy for SC use and the generally similar safety profiles with no new safety (including immunogenicity) concerns after IV administration of SB309 in cancer patients (European Medicines Agency, 2007b). Overall, the extrapolation of indications for epoetin biosimilars was based on the totality of evidence that included similar structure and function, comparable PD effects (i.e., stimulation of reticulocytes), comparable efficacy in patients with renal anemia, and comparable safety between the epoetin biosimilars and their reference product, and the similar mechanism of action in all approved indications.

5. Biosimilar monoclonal antibodies in development for oncology

Recognizing the highly complex structure of mAbs, the EMA published additional guidelines specific for mAbs to complement the original EMA guidelines for the development of biosimilars (European Medicines Agency, 2012). These guidelines state that extrapolation of clinical safety and efficacy data to other indications approved for the reference mAb is possible based on the results of the overall evidence provided in the comparability exercise and with scientific justification. A request for indication extrapolation should be supported by scientific rationale on the mechanism of action and the receptors involved in each indication. If the mechanism of action is different or unknown, other relevant data should be provided to support extrapolation of indications (European Medicines Agency, 2012). In the oncology setting, because the preferred endpoints to establish anticancer activity, i.e., progression-free/disease-free survival or overall survival, may not be feasible or sensitive enough to establish similar efficacy of the biosimilar and the reference mAbs, the EMA recommends using a clinical endpoint that measures activity as a primary endpoint (e.g., overall response rate or pathological complete response) (European Medicines Agency, 2012). To enable detection of potential product-related differences and minimize the risk for unpredictable immune responses, extrapolation of clinical data is recommended from a population that is potentially more homogenous and not immune-compromised versus a population that is less homogenous and immune-compromised (European Medicines Agency, 2012).

5.1. Trastuzumab

Trastuzumab (Herceptin® [Genentech/Roche]), a humanized recombinant mAb directed at the human epidermal growth factor receptor 2 (HER2), is indicated for the treatment of HER2-positive breast cancer in the adjuvant and metastatic setting, and for the treatment of HER2-positive metastatic gastric or gastroesophageal junction adenocarcinoma (Genentech Inc., 1998). The composition of matter patent covering trastuzumab marketed in Europe (Herceptin [Roche]) expired in 2014; the last composition of matter patent in the United States (Herceptin [Genentech]) will expire in 2019 (Philippidis, 2014). Biosimilars to trastuzumab are being developed and many are in late-stage clinical development (Table 2); all are being conducted in patients with metastatic breast cancer (MBC) or early breast cancer (EBC). Extrapolation from metastatic setting to adjuvant setting and vice versa could be justified if biosimilarity is established based on the totality of the evidence and the mechanism of action is proved to be the same in these indications. Worldwide, two biosimilars to trastuzumab have been approved: one by the Korean Ministry of Food and Drug Safety, which is marketed in South Korea (Herzuma® [Celltrion, Incheon City, Republic of Korea]) (Generics and Biosimilars Initiative (GaBI) Online, 2014a), and the other by the Drugs Controller General of India, which is marketed under two different brand names in India (Hertraz™ [Mylan, Mumbai, India] and CANMAb™ [Biocon, Bangalore, India]) (Generics and Biosimilars Initiative (GaBI) Online, 2014b,c). These biosimilars have been approved for all indications held by the reference product (Herceptin). It should be noted that biosimilars approved in India might not meet the stringent regulatory requirements for establishing biosimilarity as outlined by EMA, FDA, or WHO.

5.2. Bevacizumab

Bevacizumab (Avastin® [Genentech and Roche]) is a recombinant humanized mAb that is directed at the human vascular endothelial growth factor (VEGF) (Genentech Inc., 2004; European Medicines Agency, 2009c). Bevacizumab is approved in the European Union and United States as a component of combination therapy for the treatment of metastatic colorectal cancer, metastatic or recurrent non-squamous non-small-cell lung cancer, and metastatic renal cell carcinoma, as well as cervical, platinum-resistant recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancers. In addition, bevacizumab is approved in the European Union as a component of combination therapy for the treatment of metastatic breast cancer and in the Unites States as a single agent for the treatment of glioblastoma in adults with progressive disease following prior therapy. Approved indications may vary in other countries. The composition of matter patent covering bevacizumab marketed in the United States (Genentech) will

Table 2
Biosimilar monoclonal antibodies in development for oncology with registered phase III trials.[a]

Biosimilar name	Company	Indication tested	Status	Estimated primary completion date[b]
Biosimilars to trastuzumab (Herceptin®, Genentech)				
BCD-022	Biocad	HER2 + MBC	Ongoing, not recruiting	March 2015
PF-05280014	Pfizer	HER2 + MBC	Currently recruiting	October 2017
		HER2 + EBC (Jacobs et al., 2015)	Currently recruiting	December 2016
ABP 980	Amgen	HER2 + EBC	Currently recruiting	December 2016
CT-P6	Celltrion	HER2 + MBC (Im et al., 2013)	Ongoing, not recruiting	December 2017
		HER2 + EBC	Currently recruiting	June 2019
SB3-G31-BC	Samsung Bioepis	HER2 + early or locally advanced BC	Currently recruiting	January 2016
Hercules/Myl1401O	Mylan GmbH	HER2 + MBC	Ongoing, not recruiting	January 2016
Biosimilars to bevacizumab (Avastin®, Genentech/Roche)				
BCD-021	Biocad	NSCLC (Filon et al., 2015)	Ongoing, not recruiting	November 2015
PF-06439535	Pfizer	NSCLC	Currently recruiting	July 2017
ABP 215	Amgen	NSCLC	Ongoing, not recruiting	July 2015
Biosimilars to rituximab (Rituxan®, Genentech/Biogen Idec; MabThera®, Roche)				
BCD-020	Biocad	IndolentNHL (Alexeev et al., 2014)	Currently recruiting	December 2015
		RA	Ongoing, not recruiting	July 2015
PF-05280586	Pfizer	FL	Currently recruiting	November 2016
		RA (Williams et al., 2015)	Ongoing, not recruiting	August 2015
ABP 798	Amgen	RA	Ongoing	Not available
		NHL	Ongoing	Not available
GP2013	Sandoz	FL	Ongoing, not recruiting	December 2017
		RA	Currently recruiting	December 2016
CT-P10	Celltrion	FL	Currently recruiting	February 2017
		FL	Not yet recruiting	March 2018
		RA (Yoo et al., 2013)	Currently recruiting	January 2017
RTXM83	mAbxience	DLBCL	Currently recruiting	May 2016

BC, breast cancer; DLBCL, diffuse large B-cell lymphoma; EBC, early breast cancer; FL, follicular lymphoma; HER2, human epidermal growth factor receptor; MBC, metastatic breast cancer; NHL, non-Hodgkin's lymphoma; NSCLC, non-small-cell lung cancer, RA, rheumatoid arthritis.
[a] Registered on ClinicalsTrials.gov, the International Clinical Trials Registry Platform or the European Union Clinical Trials Register.
[b] Final data collection date for primary outcome measure.

expire in 2019; the last composition of matter patent in Europe (Roche) will expire in 2018 (Philippidis, 2014). Only a few potential biosimilars to bevacizumab are in late-stage clinical development and have a registered phase III trial (Table 2); all are being conducted in patients with non-small-cell lung cancer. At this time, no biosimilars to bevacizumab are approved.

5.3. Rituximab

Rituximab (Rituxan® [Genentech/Biogen Idec, US] and MabThera® [Roche, EU]) is a chimeric murine-human mAb directed at the CD20 antigen of B cells. Rituximab is unique as it is approved for both oncology and anti-inflammatory indications. Rituximab, in combination with glucocorticoids, is indicated for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis and granulomatosis with polyangiitis and microscopic polyangiitis in adult patients (Biogen Idec Inc., 1997; European Medicines Agency, 2009b). The composition of matter patent covering rituximab marketed in Europe (MabThera) expired in 2013; the last composition of matter patent in the United States (Rituxan) will expire in 2018 (Philippidis, 2014). Several biosimilars to rituximab are in late-stage clinical development (Table 2). Comparative clinical studies for rituximab biosimilars are conducted in various indications, including, rheumatoid arthritis, diffuse large B-cell lymphoma, and follicular lymphoma. Extrapolation of indication for rituximab may be allowed from non-malignant setting (e.g., rheumatoid arthritis) to an oncology setting, from oncology setting to autoimmune disease, from single-agent to combination therapy, or from combination to single-agent if it is scientifically justified. Recently, a biosimilar to rituximab has been approved by the Russian Ministry of Health (Acellbia™ [Biocad, Saint Petersburg, Russia]) (Generics and Biosimilars Initiative (GaBI) Online, 2014d). It should be noted that the biosimilars in Russia may not meet the stringent regulatory requirements for establishing biosimilarity as outlined by EMA, FDA, or WHO.

Approval of biosimilar mAbs may help preventing the risk of drug shortages, i.e., the supply of the reference product not meeting its demand, which could have a devastating effect on the life of patients with cancer (Li et al., 2015). The accelerated development program of biosimilar mAbs that relies on extrapolation may minimize some of the potential causes of drug shortages, including manufacturing related issues and increased demand. The availability of high-quality, safe, and effective biosimilars, developed by reliable manufacturers that follow the stringent regulatory requirements of EMA, FDA, or WHO, may ensure broader patient access to biologic therapies while preventing potential drug supply shortage.

6. Conclusions

As some of the composition of matter patents covering oncology biologic mAbs have expired or will expire in the upcoming years, approval of biosimilar mAbs for oncology indications is expected. Biosimilarity is established based on comprehensive comparability analytical, functional, non-clinical, and clinical studies. Extrapolation of indication is an integral part of the biosimilar concept; it allows manufacturers to make biologic therapies more broadly accessible within a tailored development program. Extrapolation of indication must be scientifically justified and is based on the totality of evidence from the comparability exercise with the reference product. When seeking extrapolation of indications, pivotal clinical studies to assess efficacy and safety (including immunogenicity) should be conducted in the most-sensitive patient population, using endpoints that can detect any clinically meaningful differences between the proposed biosimilar and the reference product. The goal of the clinical program is not to re-establish patient benefit but to confirm the similarity established by the structural and functional characterization. Biosimilars uptake increased dramatically across Europe since their introduction to the market, though the

uptake varies significantly among different countries (IMS Institute for Healthcare Informatics, 2014). Based on the European experience with biosimilars over the past few years, biosimilars have functioned, as expected, similar to the originator biologics, including in indications that were licensed based on extrapolation.

Contributors/authorship

All authors prepared the article and approved the final draft for submission.

Competing financial interests

Giuseppe Curigliano has no conflict of interest to declare or financial disclosure. Darran O'Connor received consultancy fees from Pfizer Inc. Julie A. Rosenberg and Ira Jacobs are employees of and hold stock and stock options in Pfizer Inc.

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