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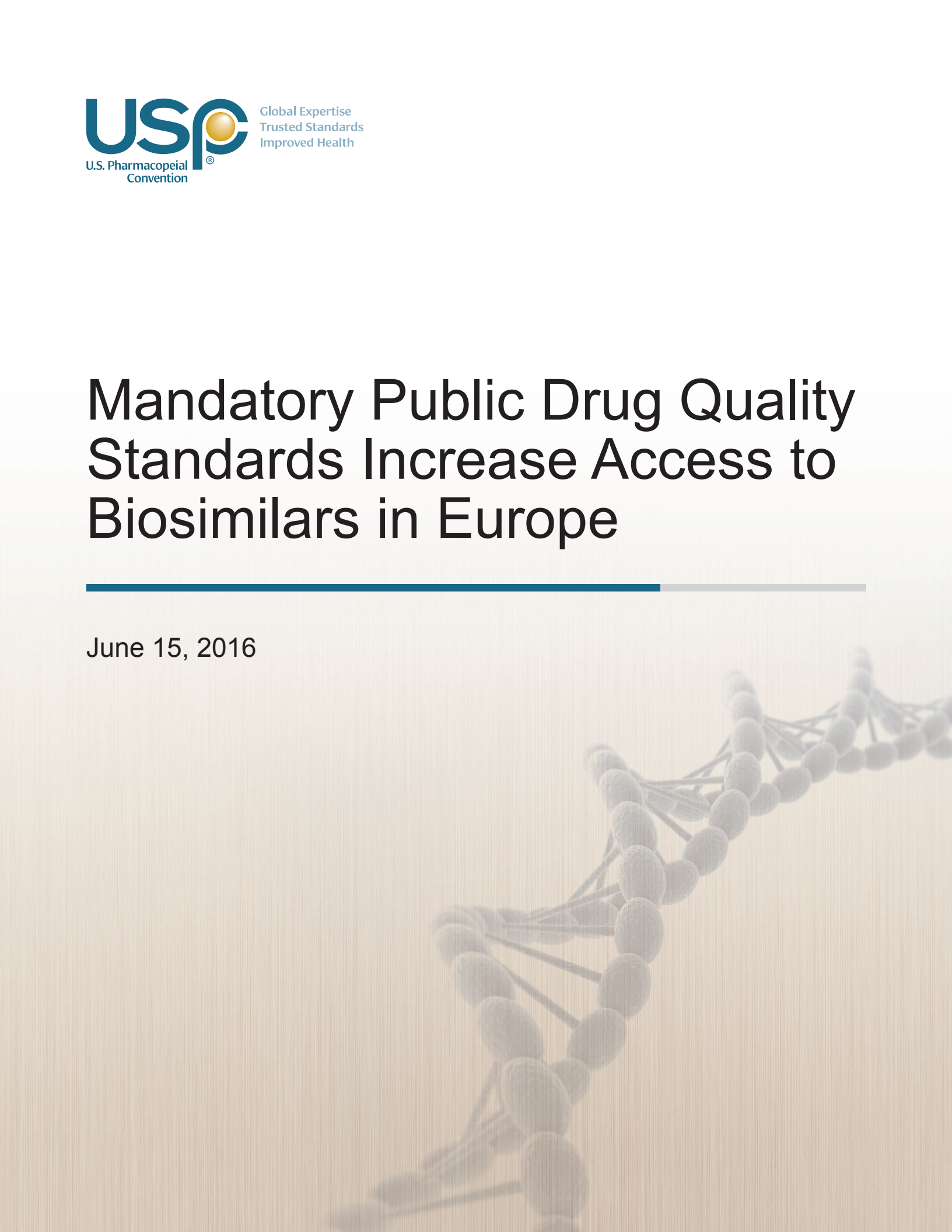

Mandatory Public Drug Quality Standards Increase Access to Biosimilars in Europe

Countries around the globe rely on public standards of quality as an important regulatory component to ensure patient safety and increase access to quality medicines. In Europe, the drug regulatory system has linked public quality standards to biosimilar approvals for over a decade. Data shows that manufacturers in Europe utilize public quality standards in product development and cite them in their regulatory approval applications. This has helped foster a vibrant biosimilar marketplace and provides a model for consideration as the U.S. continues to implement its biosimilar regulatory framework.

Background

Mandatory public standards of quality[1] are developed by pharmacopeias such as the United States Pharmacopeia (USP), the European Pharmacopeia (Ph. Eur.) or the World Health Organization (WHO) and enable pharmaceutical companies to more efficiently develop and manufacture drugs, including biological products.[2] Relying on public standards facilitates regulatory approval and eliminates costly and time-consuming duplication of efforts because manufacturers are no longer required to develop their own methods for testing product quality and rather rely on a public standard. Public standards also promote competition by supporting the entry of multiple manufacturers into the market for biological products, similar to what has been observed with the market for generic drugs. This is an important driver in increasing access to quality medicines for patients while decreasing overall healthcare cost.

Pharmacopeias and regulatory authorities work along with industry, academe and other health and science organizations to publicly and collaboratively develop and update standards. Historically, drug approvals in the U.S. and Europe have relied on public standards to accelerate drug development and approval in multi-manufacturing environments. If a product submitted for regulatory approval complies with the existing monograph (i.e., the public standard), regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Authority (EMA) traditionally accept this compliance as sufficient to demonstrate certain quality attributes. While public standards provide the underpinning for the quality assessment of the product, final approval and determination of sameness or equivalence are made solely by regulatory authorities.

Europe Leads in Biosimilars While Requiring Compliance with Independent Public Standards for Biologicals

In the European Union, a regulatory framework for biosimilars was established in 2003, paving the way for the approval of over twenty biosimilar products. While many factors have contributed to the success of the biosimilar market in Europe, public standards for the quality of biologicals have played an important role in facilitating product development, ensuring regulatory predictability, and enhancing patient and provider confidence. In the U.S., Congress enacted the *Biologics Price Competition and Innovation Act* (BPCIA) in 2010.[3] To date two biosimilar products have been approved.

A review of approval documents from EMA show that public standards and complementary reference materials were frequently used as tools for biosimilar development. In fact, the approval documents for **21 biosimilars (those that were approved in Europe and not later withdrawn – see table below) refer to the manufacturer's use of European Pharmacopeia and international public standards, including reference standards, in the development of these products.**[4]

The European example shows how public standards for biosimilars and biologics play a critical role in:

1. ensuring patient and provider confidence in the quality and safety of these new products,
2. facilitating competition and the entry of multiple manufacturers by providing cost-effective tools, e.g., a common benchmark for quality for manufacturers to use[5],
3. accelerating regulatory approvals,
4. reducing overall healthcare costs.

Europe is the forerunner for the biosimilars market and the EMA has implemented a well-established legal and regulatory pathway for the approval of biosimilar products through a series of guidelines. EMA guidelines for biologics, as well as those for biosimilars, recommend the use of international standards[6] in their development. Furthermore, the National Institute for Biological Standards and Control (NIBSC) in the UK has supported the use of public standards.[7] Notably, EMA's guidelines for biosimilar development explain that biologics are more complex and sensitive to changes in manufacturing, compared to chemically-derived products, so "the safety/efficacy profile of these products is highly dependent on the robustness and the monitoring of quality aspects."[8] With this point in mind **biosimilars are required to satisfy "the technical requirements of the monographs of the European Pharmacopoeia"[9] with regard to quality data.**

The monographs of the Ph. Eur. include quality specifications for many unfinished products or "drug substances" as well as for some finished products. Monographs in the European Pharmacopoeia exist for many approved biosimilars—e.g., human growth hormone (somatropin), erythropoietin (epoetin), filgrastim, and insulin.[10] In addition, the Ph. Eur. contains general monographs (similar to general chapters in the USP) that cover product class quality aspects, e.g., for monoclonal antibodies and low molecular weight heparins. According to EMA, "[a]nalytical procedures, where appropriate are the ones described in the monographs. The test procedures are considered qualified as they are described in the compendial monographs."[11] Therefore, compliance with the procedures and tests reflected in the monograph establishes the key components of the quality of the product.

Europe utilizes public standards for numerous quality-related purposes including characterization/qualification of drug substances as well as standards for activity measurement, which is important for dosing strategies and dosing.

Standards for Characterization and Qualification

Characterization refers to analysis of the physical, chemical, and biological properties of the active components in biological drug substances. Chemical reference standards are often used to establish the identity of the material or to measure the molecular variants of the medicinal products. The use of standards is critical to establish and control the limits of variants.

EMA recommends that sponsors use an international or Ph. Eur. standard as a primary reference material to characterize their biologic products.[12] Sponsors of both biosimilars and biologics approved in Europe use Ph. Eur. product monographs and associated reference standards, WHO/NIBSC standards, USP standards, and/or in-house methods to characterize their product and develop specifications for both the drug substance and the final drug product.[13] Note that sponsors do have the option of using their in-house standards, among other standards, and therefore they are not limited to compendial (pharmacopeial) methods.[14] EMA does recommend, however, that biologics sponsors use international or national reference standards, when appropriate, to calibrate in-house working reference material.[15] This demonstrates a key point: the existence of a public standard does not limit sponsors' options, impede product development, or thwart innovation.

Furthermore, to demonstrate biosimilarity (or "comparability" in Europe[16]) to a reference product, it is necessary to perform extensive, head-to-head studies using state-of-the-art methods. Thus the biosimilar sponsor must show that the analytical and functional assays used to demonstrate biosimilarity/comparability can "detect slight differences in all aspects pertinent to the evaluation of quality (e.g., ability to detect relevant variants with high sensitivity)."[17] EMA recommends that standards and reference materials (e.g., from EP, WHO) should be used for method qualification and standardization.[18]

Many examples exist of sponsors using various public standards to validate their methods for obtaining the extensive analytical evidence of biosimilarity/comparability that is needed for approval. Examples include the use of reference standards from Ph. Eur. and/or NIBSC/WHO for somatropin biologics and biosimilars[19], and use of WHO or Ph. Eur. standards to validate assays for insulin products.[20]

Standards for Activity/Dosing

Dosing refers to the amount of active (bioactive) substance given to a patient, the so-called "potency" of a biologic. While many modern medicines carry the amount of a medicine in weight on their labels, very often the dose given to a patient is measured by the activity/potency rather than just the weight. This activity is generally expressed in units and often linked to an international standard established by WHO. Well-known examples are insulins and heparins that are, to this day, dosed in units/mg of biologic. The measurement of activity is achieved by the use of test methods where the product is tested against an established public standard (e.g. WHO international standard, or pharmacopeial standard such as the Ph. Eur. and USP's). These standards are called bioassay standards as they allow measurement of units of activity, and these units are important for dosing strategies.

EMA also recommends in their biosimilar guidelines that "[t]he results of relevant biological assay(s) should be provided and expressed in units of activity calibrated against an international or national reference standard, when available and appropriate. These assays, whether proprietary or represented in a public monograph, should comply with appropriate European Pharmacopoeia requirements for biological assays, if applicable."[21]

Obtaining accurate data on units of activity for biosimilars is critical and impacts appropriate labeling and safe use of all biologics, NIBSC states.[22] For example, the sponsor of Apidra® (insulin glulisine), an originator biologic, used a bioassay method and a human insulin reference standard, both from USP, to accurately determine the units of activity for their product.[23] In some cases, public standards can resolve an issue preventing approval of a product, as the sponsor of the biosimilar Nivestim® (filgrastim) learned when they were asked to adapt their specifications according to EP. This led to resolution of a major objection regarding the potency of their clinical material—the major issue holding up regulatory approval.[24]

From the examples cited above, and others not mentioned here for brevity, it is clear that biosimilars sponsors—just like sponsors of originator biologics—appropriately rely on public standards (monographs, general methods, and reference standards) as critical tools that allow them to develop their biological products efficiently. Avoiding a need to reinvent methods is a major benefit to biologics manufacturers, saving time, effort, and money while also enhancing quality for the patient. Ultimately, public standards foster transparency and enhance all stakeholders' confidence in approved and marketed biologics.

Conclusion:

Historically, pharmacopeias including USP and regulatory agencies including FDA—along with manufacturers—have collaborated globally and should continue to work together to develop product-specific monographs, reference standards, and general methods that can be relied upon by manufacturers and regulatory agencies. These goals currently apply to both drugs and biologics, with the pharmacopeias making no decisions as to the regulatory routes to approval.

Given that the sponsors of all biosimilars approved in Europe relied on public standards to develop their products, the existence of such quality standards is clearly useful and beneficial. Public standards help sponsors develop biosimilars (and all biologics) more quickly, efficiently, and at lower cost, enabling multi-manufacturer markets for biological products. This helps close the gap for unmet patient needs, ensure the safety of medications and reduce overall healthcare costs.

Table 1: Biosimilar Approvals (not withdrawn) in the EU

Medicine Name	Active Substance	Marketing Authorisation Holder	Authorisation Date
Abasaglar (previously Abasria)	insulin glargine	Eli Lilly Regional Operations GmbH	09/09/2014
Abseamed	epoetin alfa	Medice Arzneimittel Pütter GmbH & Co. KG	28/08/2007
Accofil	filgrastim	Accord Healthcare Ltd	18/09/2014
Bemfola	follitropin alfa	Finox Biotech AG	27/03/2014
Benepali	etanercept	Samsung Bioepis UK Limited	14/01/2016
Binocrit	epoetin alfa	Sandoz GmbH	28/08/2007
Biograstim	filgrastim	AbZ-Pharma GmbH	15/09/2008
Epoetin Alfa Hexal	epoetin alfa	Hexal AG	28/08/2007
Filgrastim Hexal	filgrastim	Hexal AG	06/02/2009
Flixabi	infliximab	Samsung Bioepis	26/05/2016
Grastofil	filgrastim	Apotex Europe BV	18/10/2013
Inflectra	infliximab	Hospira UK Limited	10/09/2013
Nivestim	filgrastim	Hospira UK Ltd	08/06/2010
Omnitrope	somatropin	Sandoz GmbH	12/04/2006
Ovaleap	follitropin alfa	Teva Pharma B.V.	27/09/2013
Ratiograstim	filgrastim	Ratiopharm GmbH	15/09/2008
Remsima	infliximab	Celltrion Healthcare Hungary Kft.	10/09/2013
Retacrit	epoetin zeta	Hospira UK Limited	18/12/2007
Silapo	epoetin zeta	Stada Arzneimittel AG	18/12/2007
Tevagrastim	filgrastim	Teva GmbH	15/09/2008
Zarzio	filgrastim	Sandoz GmbH	06/02/2009

[1] A public quality standard generally has two components: a monograph (documentary standard) and a reference standard. USP's monographs appear in the *United States Pharmacopeia—National Formulary (USP–NF)* and include tests and procedures that establish the identity, strength, quality and purity of drug products and active pharmaceutical ingredients. Reference standards are physical reference materials that are used by manufacturers to ensure that their products meet monograph requirements. Together, monographs and reference standards comprise the public standards which are the quality safety net to protect patients and ensure quality medicines. In addition, general chapters add flexibility by offering choices of analytical approaches or they help a manufacturer bridge and transition between methods. Importantly in the biologics space, the general chapters and associated reference standards provide significant help in early development to manufacturers who are new to a particular product area. Chapters and reference standards complement product-specific development efforts by providing sound performance criteria for quality assessment methodologies. Often they can also provide an important entry point for new technology into the compendium, making it accessible to the entire industry.

[2] The World Health Organization (WHO) re-emphasized the importance of these standards for therapeutics manufactured globally. The WHO establishes international standards for the measurement of biological potency (activity), a key factor in the assessment of biological medicine. WHO International Standards for Biotherapeutic Products, May 2016, available at: http://www.who.int//biologicals/BiologicalstandardsQAfinal.pdf (accessed June 14 2016).

[3] The US statute creating a biosimilar pathway in the US (the BPCIA) was enacted in 2010, 7 years after a biosimilars regulatory pathway was created in Europe. TITLE VII: IMPROVING ACCESS TO INNOVATIVE MEDICAL THERAPIES. Subtitle A: Biologic Price Competition and Innovation (BPCI Act) provisions of the Patient Protection and Affordable Care Act (PPACA), (2010) Pub.L.111-148, 124 Stat. 817, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf (accessed June 14, 2016).

[4] Even the absence of an explicit reference to public standards in approved documents does not indicate that public standards were not used in product development. Public standards are frequently utilized but not specifically noted or cited in public portions of applications.

[5] Comments of NIBSC on "Draft Guidance for Industry on Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product," August 8, 2014, available at: https://www.regulations.gov/#!documentDetail;D=FDA-2014-D-0234-0008 (accessed June 14 2016).

[6] See e.g., EMA Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials, EMA/CHMP/BWP/534898/2008, February 18, 2010, available at: http://ec.europa.eu/health/files/eudralex/vol-10/2012-05_quality_for_biological.pdf (accessed June 14, 2016); EMA, Guideline on similar biological medicinal products, October 23, 2014, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf (accessed June 14, 2016).

[7] The National Institute for Biological Standards and Control (NIBSC) in the UK has stated that the use of "[public standards] provide an independent single reference point for measuring the potency of products manufactured at different times and in different places, and hence are critical for maintaining global standards of quality and efficacy." Comments of NIBSC on "Draft Guidance for Industry on Clinical Pharmacology Data to Support a Demonstration Biosimilarity

to a Reference Product," August 8, 2014, available at: https://www.regulations.gov/#!documentDetail;D=FDA-2014-D-0234-0008 (accessed June 14, 2016).

[8] EMA, Guideline on similar biological medicinal products, October 23, 2014, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf (accessed June 14, 2016).

[9] EMA, Guideline on similar biological medicinal products, October 23, 2014, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf (accessed June 14 2016); Product specific EMA guidelines also reference the utility of standards, e.g., Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (Revision), March 18, 2010, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/04/WC500089474.pdf (accessed June 14 2016), ("Information on the erythrogenic activity may be obtained from the described repeat dose toxicity study or from a specifically designed assay (e.g., the European Pharmacopoeia normocythaemic mouse assay; data may be already available from quality-related bioassays)").

[10] S. Wicks, "Ensuring the Quality of Biologicals," *BioPharm International* 28 (5) May 2, 2015, available at: http://www.biopharminternational.com/ensuring-quality-biologicals-0?__hstc=79483275.a5e638b709bf2364c6ebc89b1a6887d7.1462808333428.1462808333428.1462808333428.1&__hssc=79483275.2.1462808333429&__hsfp=2617444982 (accessed June 14 2016).

[11] EMA, Scientific Discussion for Omnitrope, April 25, 2006, available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000607/WC500043692.pdf (accessed June 14 2016).

[12] See e.g., EMA Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials, EMA/CHMP/BWP/534898/2008, February 18, 2010, available at: http://ec.europa.eu/health/files/eudralex/vol-10/2012-05_quality_for_biological.pdf (accessed May 26, 2016).

[13] See e.g., EMA, Assessment Report for Somatropin Biopartners, May 30, 2013, available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002196/WC500148755.pdf (accessed June 14 2016); EMA, Scientific Discussion for NutropinAq, July, 12, 2006, available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000315/WC500040081.pdf (accessed June 14 2016); EMA, Scientific Discussion for Omnitrope, April 25, 2006, available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000607/WC500043692.pdf (accessed June 14 2016).

[14] See e.g., EMA, Assessment Report for Somatropin Biopartners, May 30, 2013, available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002196/WC500148755.pdf (accessed June 14 2016) ("The validation of non-compendial analytical methods is considered acceptable.").

[15] EMA Guideline ICH Topic Q 6 B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, Step 5, CPMP/ICH/365/96, September 1999, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002824.pdf (accessed May 26, 2016).

[16] M. Weise et al, "Biosimilars: the science of extrapolation," *Blood* 124 (22) November 20, 2014, available at: http://www.bloodjournal.org/content/124/22/3191?sso-checked=true (accessed June 14 2016).

[17] EMA, Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1), May 22, 2014, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167838.pdf (accessed June 14 2016).

[18] EMA, Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1), May 22, 2014, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167838.pdf (accessed June 14 2016).

[19] See e.g., EMA, Assessment Report for Somatropin Biopartners, May 30, 2013, available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002196/WC500148755.pdf (accessed June 14 2016); EMA, Scientific Discussion for Omnitrope, April 25, 2006, available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000607/WC500043692.pdf (accessed June 14 2016); EMA, Scientific Discussion for NutropinAq, July, 12, 2006, available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000315/WC500040081.pdf (accessed June 14 2016).

[20] See e.g., EMA, Scientific Discussion for Apidra, October, 21, 2005, available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000557/WC500025246.pdf (accessed June 14 2016).

[21] EMA, Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1), May 22, 2014, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167838.pdf (accessed June 14 2016).

[22] NIBSC, Comments of NIBSC on "Draft Guidance for Industry on Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product; Availability," August 8, 2014, available at: https://www.regulations.gov/#!documentDetail;D=FDA-2014-D-0234-0008 (accessed June 14 2016), ("A key component of the comparability exercise necessary to establish biosimilarity will usually be demonstration of appropriate biological activity in a test model (bioassay). WHO International Biological Standards are specifically designed for standardisation of such quantitative bioassays. The reference standards have defined potency and are carefully tested a ent single reference point for measuring the potency of products manufactured at different times and in different places, and hence are critical for maintaining global standards of quality and efficacy.").

[23] EMA, Scientific Discussion for Apidra, October, 21, 2005, available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000557/WC500025246.pdf (accessed June 14 2016), ("The Ph.Eur. recommends the use of international units for human insulins but not for insulin analogues. ICH Q6B states that in case there is no international reference standard for a biological molecule, the potency of the molecule should be calculated against a characterised in-house reference material and the results should be reported as in-house units.").

[24] EMA, CHMP Assessment Report for Nivestim, June, 23, 2010, available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001142/WC500093664.pdf (accessed June 14 2016).