June 5, 2019

Senate Committee on Health, Education, Labor and Pensions (HELP)
428 Senate Dirksen Office Building
Washington, DC 20510

Dear Members and staff of the Senate HELP Committee:

Attached please find United States Pharmacopeia's (USP) comments on the discussion draft of the HELP Committee's Lower Health Care Costs Act of 2019.

We welcome the chance to address any questions or concerns. Please feel free to contact me at apl@usp.org or (301) 816-8336 or Joseph Hill, Director, US Government Affairs, at joe.hill@usp.org or 202-239-4137.

Sincerely,

Anthony Lakavage, JD
Secretary, USP Convention and Board of Trustees
Senior Vice President, Global External Affairs
USP

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The United States Pharmacopeia (USP)[1] appreciates the opportunity to comment on the discussion draft of the HELP Committee's Lower Health Care Costs Act of 2019. We commend the Committee for seeking to advance mechanisms to help ensure the provision of affordable, safe, quality healthcare and medicines for consumers and patients. However, USP opposes inclusion of Section 207, Biological Product Innovation, because it will not achieve the Committee's intent to lower healthcare costs and will jeopardize patient safety. **Our concerns are shared by numerous patient, healthcare practitioner, and industry groups.** See *Attachment 1*.

Section 207 would unravel a critical piece of the overall safety net for biologics, impede competition, diminish transparency and accountability, and decrease the public's trust in these therapies. **In the interest of ensuring patient safety and access to quality medicines, Section 207 or any other similar provision should not be included in any future legislation.**

Adherence to public quality standards is essential to ensuring patient safety and protecting the public's health.

For nearly 100 years, the framework to safeguard the quality and safety of medicines in the United States has been based on the principle that compendial standards, required under the law, represent quality expectations that are transparently established with public participation.[2] This approach has been widely effective in safeguarding patient safety for millions of Americans and should not be undermined as proposed in Section 207.

Public quality standards[3] play a fundamental role in protecting the safety of American patients. The benchmarks in a USP public quality standard allow for independent determination that a product has been made according to regulatory expectations regardless of the manufacturer or manufacturing process. As past experience has shown, during times of crisis, public standards can help respond to public health needs.[4] Section 207 would compromise this rapid response capability and instead generate the need for lengthy and cumbersome legislative or regulatory processes to effect quality requirements, which could potentially put patients at risk.

Public quality standards remain essential because Americans increasingly receive biologics from a complex, growing global supply chain. There is a critical need for a common public standard to assure the quality and consistency of biologic medicines moving in national and global commerce. And because of today's globalized marketplace, adherence to public quality standards is essential as they are used by numerous entities to test for quality at any point along the supply chain.

Consider insulin, for example. USP, working with stakeholders, has developed public standards for insulin that help ensure product quality, regardless of the source (i.e., sourced naturally from animals or made recombinantly). Since the introduction of the first official USP insulin standard in 1941, USP has developed and updated numerous insulin public quality standards, making insulin in the United States among the safest in the world.[5] See *Attachment 2, List of USP Public Quality Standards Related to Insulin*. Section 207 would remove requirements that help ensure the quality and safety of

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medicines such as insulin. When it comes to our families' health, the quality and safety of our medicines are not optional.

Public quality standards are scientifically based and facilitate multi-manufacturing, approval of biologics, and innovation.

While Section 207 is being presented as necessary to promote innovation and reduce the cost of biologic medicines, this is not the case. In fact, a public standard promotes competition and multi-manufacturing, thus increasing access to quality medicines. Furthermore, USP standards are scientifically based, flexible to evolve with public health needs, and have been continuously revised and modernized to accommodate innovation and technological advances since the first publication of the USP compendia.

As medicines have evolved and scientific knowledge has advanced, USP has been there to support and encourage these advancements, utilizing the work of scientific experts and a network of sophisticated laboratories.[6] In this year alone, over 800 individual experts and 100 government liaisons have participated in USP standards-setting committees that continuously advance the science and technology of quality standards.[7] USP also has robust processes to continuously align standards in a timely manner with regulatory expectations, preventing compliance concerns while supporting innovation.[8]

USP public standards help manufacturers bring medicines to market and help facilitate access to quality biologics for patients. Biologic medicine developers use public quality standards to establish the key attributes of their products. In this way, USP's public standards facilitate the entry of products from multiple manufacturers, promoting competition and access.

Standards also foster regulatory certainty around quality. Countries around the world rely on adherence to public quality standards as an important regulatory component to ensure patient safety and increase access to quality medicines. Robust biosimilar markets exist in the European Union (EU) and elsewhere, where compendial standards are intrinsic parts of the regulatory ecosystem. To date, there have been over 50 biosimilar products approved in the EU.[9] While many factors have contributed to the success of the biosimilar market in Europe, public standards for the quality of biological products have played an important role in facilitating product development. See *Attachment 3, Mandatory Public Drug Quality Standards Increase Access to Biosimilars in Europe*.

Public quality standards provide transparent expectations and accountability for quality across stakeholders.

At a time when we need to build the public's trust in biologics, we need more transparency and accountability, not less. Public standards, developed through a transparent, open and multi-stakeholder process, articulate the key quality attributes to which everyone is held accountable.[10] This system facilitates trust in biologic medicines across the healthcare ecosystem. Standards underpin the confidence that is essential for physician prescribing. They provide information that is important to the practice of

pharmacy and pharmacists' engagement with patients. They lay the groundwork for trust that facilitates patient adoption of new therapies.

Without USP's public standards, key quality attributes generally would not be available to industry, healthcare practitioners, health authorities, and patients. Removing this transparency would undermine public trust in biologic medicines. Specifically,

- Manufacturers would not have public quality attributes to which they can hold themselves and others accountable, removing a linchpin protecting the quality of the global supply chain;
- Public health authorities would not have access to a publicly available standard to evaluate the quality of a medicine; and
- Trust in the quality of biologic medicines would be undermined across the healthcare ecosystem – from prescribers to patients.

Section 207 would weaken the safety net that protects our medicines and the patients who use them. If the proposal were adopted, there would be no required adherence to public quality standards for products such as insulin, potentially jeopardizing the uniformity and quality of these medicines and the health of patients. This is particularly concerning as policymakers work to diversify the market for these products and help ensure accessible, lower-priced, safe, quality products.

We appreciate the opportunity to comment on this important issue and reiterate our request that Section 207 or any other similar provision not be included in any future legislation.

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[1] USP is an independent, nonprofit, scientific organization governed by a Convention comprising over 450 leading organizations and institutions in health and science from the public sector; academia; industry; healthcare practitioners; and consumer and patient communities.

[2] This framework has been in existence since the enactment of the Federal Food, Drug, and Cosmetic Act (FD&C Act) in 1938. This federal law requires that a drug must comply with applicable USP public quality standards for identity, strength, quality, and purity. Biologics regulated under the Public Health Service Act (PHS Act) are subject to the drug regulatory requirements of the FD&C Act, which means they are required to comply with the adulteration and misbranding provisions of the FD&C Act, including *United States Pharmacopeia–National Formulary (USP–NF)* compendial requirements.

[3] A public quality standard for a biologic medicine is a benchmark that consists of tests and other measures to determine a medicine's identity, purity, and potency, and often includes additional requirements relating to labeling and storage, such as the appropriate environmental conditions (e.g., temperature) that could determine whether a product will degrade during distribution. A public quality standard helps ensure consistent potency regardless of the manufacturer or manufacturing process and regardless of whether a facility is in the United States or overseas.

[4] For example, at the request of the U.S. Surgeon General, USP helped respond to a public health crisis involving tainted vaccines, by creating one of the very first public standards for a biologic: diphtheria antitoxin (1902).

[5] USP comments on the "The Future of Insulin Biosimilars: Increasing Access and Facilitating the Efficient Development of Insulin Biosimilar and Interchangeable Products;" Public Hearing; Request for Comments (Docket No. FDA-2019-N-1132) (submitted May 31, 2019).

[6] With more than 185,000 square feet of laboratory space in five countries, including Ghana, India, and China, laboratories are at the heart of USP's work. As part of our long-standing commitment to share our expertise with other laboratories around the world, USP has supported and shared knowledge with more than 90 laboratories in over 30 countries to help build and maintain strong quality management systems aligning with international standards and practices.

[7] USP's standards-setting process is collaborative, transparent, and science-driven. USP Expert Committees are responsible for developing and revising USP public quality standards. Expert Committees are composed of independent experts from industry, government, and academia who volunteer their time and expertise as part of an open, rigorous, objective process to develop new quality standards and update existing standards.

[8] The Pending Monograph Process (PMP) enables publication of monographs for qualified articles based on monograph sponsor-provided information from applications filed with FDA. The PMP was developed through a collaboration between USP and FDA as a practical way to expedite monograph development and revision based on new applicants' specifications provided in applications submitted to the FDA. The resulting PMP also was informed by feedback from stakeholders on USP's former process. See https://www.uspnf.com/pending-monographs.

[9] See https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview.

[10] The USP Expert Committee drafts a proposed USP quality standard, which is published for public comment in the *Pharmacopeial Forum* (*PF*), USP's mechanism to solicit public comments on standards under development. The *PF* is available free of charge and is accessible from USP's website. During a comment period lasting a minimum of 90 days, USP seeks input on the proposed quality standard. The standard is adjusted based on Expert Committee evaluation and consideration of the public comments. The USP Expert Committee then votes on the standard, and if adopted by a majority vote of the Committee, the standard is published in the *USP-NF*. USP standards are in a continuous process of review and revision based upon new scientific evidence, emerging public health concerns, and public requests for revision. USP follows the same process to update and revise its standards.

May 28, 2019

The Honorable Lamar Alexander
Chairman
Senate Committee on Health, Education, Labor and Pensions
455 Dirksen Senate Office Building
Washington, DC 20510

The Honorable Patty Murray
Ranking Member
Senate Committee on Health, Education, Labor and Pensions
154 Russell Senate Office Building
Washington, DC, 20510

Dear Chairman Alexander and Ranking Member Murray:

On behalf of the undersigned organizations, we write to express urgent concern about a proposal[1] in the President's budget request that would undermine trust in the quality of biologic medicines with healthcare practitioners and patients, including for medicines widely prescribed to treat diabetes, rheumatoid arthritis, cancer, Crohn's disease and colitis, and other diseases. The proposal, contained in the HELP discussion draft, would exclude biologic medicines from the requirement that all medicines marketed in the United States adhere to quality standards established by the United States Pharmacopeia (USP). We believe that USP standards have been, and should remain, a foundational element in the framework ensuring that the medicine supply in the United States is among the safest in the world.

In the last Congress, a similar proposal was rejected after robust engagement from numerous stakeholders during consideration of the 21st Century Cures Act. We are alarmed that the proposal is being reexamined and could find its way into legislation to be considered by the HELP or Appropriations Committees this year. We respectfully urge that this proposal not be further considered and not be included in any legislation amending the Public Health Service Act (PHSA) or any other provision of law or appropriations legislation.

The proposal set forth in the President's budget request is framed as one that will lower drug costs by accelerating the development of biologic medicines, including biosimilars, with no data or rationale to support such a statement. We urge Congress to focus on resolving issues that could accelerate the availability of affordable, quality medicines for patients rather than reexamining this proposal, which poses a risk to the quality of medicines and could potentially hinder patient access.

Public quality standards are essential for ensuring the quality of medicines for patients and the practitioners who prescribe, dispense, and administer them. USP's public quality standards are established by independent, scientific experts from government, academia, industry, and the healthcare practitioner and patient communities. USP standards also go through a transparent public comment process. They provide manufacturers with key attributes of a quality medicine, as well as tests, methods, and other information that supports medicine development and manufacturing, and therefore contribute to a more efficient and reliable medicine supply.

[1] https://www.whitehouse.gov/wp-content/uploads/2019/03/FY20-Fact-Sheet_Lowering-Drug-Pricing-and-Payment_FINAL.pdf

USP, and the independent science experts on USP standard-setting committees, work in close collaboration with industry, government agencies, and healthcare practitioners. **USP's commitment to a collaborative process and its assurances that it will not publish a new biologic product monograph standard as official (and thereby enforceable) without FDA support, is well documented (www.usp.org/biologics/development-process).**

If enacted, the proposal to eliminate the requirement that biologic products comply with USP quality standards would have broad negative consequences to public health. Product developers would no longer be able to rely upon USP standards for product development, public health authorities would not have access to a publicly available standard to utilize in crisis situations, the pharmacy community would not have access to information that is important to the practice of pharmacy, and patients' trust in the quality of their medicines would be undermined.

We note that in Europe, where compliance with public quality standards is required for biosimilars, as well as for the original biologics, there have been 58 biosimilars approved to date, compared to only 19 approved in the US. In Europe, biosimilars have enabled more patients to be treated, often earlier in their disease, with no change in clinical outcomes.

There is no compelling or credible reason to change the law to remove USP from the framework that has protected Americans for 80 years. To remove USP would handicap future leaders across government who may have a perspective that is different than current Agency leadership, and who may wish to leverage USP standards in the future. We encourage continued collaboration on establishing relevant standards to ensure the quality of the medicine supply in the United States and support public health overall. We look forward to working with Congress and stakeholders on constructive solutions to ensure that Americans have access to affordable quality medicines.

Sincerely,

Academy of Managed Care Pharmacy
American Cancer Society Cancer Action Network, Inc.
American Diabetes Association
American Pharmacists Association
American Society of Consultant Pharmacists
Arthritis Foundation
ASHP (American Society of Health-System Pharmacists)
Association for Accessible Medicines
National Community Pharmacists Association
National Council for Prescription Drug Programs
United States Pharmacopeia

Attachment 2: List of USP Public Quality Standards Related to Insulin

Table 1 – USP Insulin Drug Substance Monographs

Insulin Drug Substance Monograph	Reference Standard	Date of Admission of First Standard (official date)	Date of Most Recent Revision
Insulin	Insulin Pork (50 mg) Insulin (Beef) (50 mg) Endotoxin (10,000 USP Endotoxin Units) High Molecular Weight Insulin Human (8.4 mg)	April 1, 2002 (Official Date in USP-NF) History is that it was transferred from NF May 1, 1978. First published in USP 19	March 2019 – May 2019 revision bulletin
Insulin Human	Endotoxin (10,000 USP Endotoxin Units) Insulin Human (100 mg) Insulin Pork (50 mg)	January 1, 1985 (Official)	2016 USP 39 NF34
Insulin Apsart	Insulin Aspart (7.62 mg)	May 1, 2018 (Official) Published in compendium January 6, 2014, but several revisions without becoming official until May 1, 2018	2017 USP40-NF35 2S
Insulin Lispro	Insulin Lispro (5.73 mg) Endotoxin (10,000 USP Endotoxin Units) Insulin Human (100 mg)	April 1, 2003 (Official)	Jan. 2019 Interim Revision Announcement
Insulin Glargine	Insulin Glargine (15.06 mg) Insulin Glargine for Peak Identification (3.2 mg) (Mixture of Insulin Glargine and 0A-Arg-Insulin Glargine)	May 1, 2015 (Official)	Nov. 2016 Interim Revision Announcement (IRA)

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Table 2 – USP Insulin Drug Product Monographs

Insulin Drug Product Monograph	Reference Standard	Date of Admission of First Standard	Date of Most Recent Revision
Extended Insulin Zinc Suspension	Insulin (Beef) (50 mg) Endotoxin (10,000 USP Endotoxin Units) Insulin Pork (50 mg)	September 1, 1965 (first Official Date)	Mar. 2019 – May 2019 Revision Bulletin
Human Insulin Isophane Suspension And Human Insulin Injection	Insulin Human (100 mg) Endotoxin (10,000 USP Endotoxin Units)	August 1, 2007 (official)	Jan. 2019 Interim Revision Announcement (IRA)
Insulin Zinc Suspension	Insulin (Beef) (50 mg) Endotoxin (10,000 USP Endotoxin Units) Insulin Pork (50 mg)	May 1, 2019 (Official) October 1, 1960 (First official date)	Mar. 2019 – May 2019 Revision Bulletin Official May 1, 2019
Insulin Lispro Injection	Endotoxin (10,000 USP Endotoxin Units) Insulin Lispro (5.73 mg)	April 1, 2003	Jan. 2019 Interim Revision Announcement (IRA)
Insulin Injection	Insulin (Beef) (50 mg) Endotoxin (10,000 USP Endotoxin Units) Insulin Pork (50 mg)	April 1, 2002 (First official date- Insulin Injection monograph in 1930 in *USP XI*	Mar 2019-May 2019 Revision Bulletin Official May 1, 2019
Extended Insulin Zinc Suspension	Insulin (Beef) (50 mg) Endotoxin (10,000 USP Endotoxin Units) Insulin Pork (50 mg)	September 1, 1965 (First official date)	Mar. 2019 – May 2019 Revision Bulletin (omission of USP Insulin Beef RS)
Prompt Insulin Zinc Suspension	Insulin (Beef) (50 mg) Endotoxin (10,000 USP Endotoxin Units) Insulin Pork (50 mg)	September 1, 1965 (First official date)	Mar. 2019 – May 2019 Revision Bulletin
Insulin Aspart Injection	Insulin Aspart (7.62 mg)	First Official, August 1, 2014	January 1, 2019, IRA

Insulin Drug Product Monograph	Reference Standard	Date of Admission of First Standard	Date of Most Recent Revision
Isophane Insulin Human Suspension	Endotoxin (10,000 USP Endotoxin Units) Insulin Human (100 mg) Insulin Pork (50 mg)	First Official, May 15, 1995	Jan. 2019 Interim Revision Announcement (IRA)
Insulin Human Injection	Endotoxin (10,000 USP Endotoxin Units) Insulin Human (100 mg) Insulin Pork (50 mg)	January 1, 1985 (first official date)	2015 USP38-NF33 2S
Insulin Lispro Injection	Endotoxin (10,000 USP Endotoxin Units) Insulin Lispro (5.73 mg)	April 1, 2003 (first official date)	Jan. 2019 Interim Revision Announcement (IRA)
Insulin Glargine Injection	Insulin Glargine for Peak Identification (3.2 mg	May 1, 2015 (first official date)	Nov. 2016 Interim Revision Announcement (IRA)
Isophane Insulin Suspension	Insulin Pork (50 mg) Insulin (Beef) (50 mg) Endotoxin (10,000 USP Endotoxin Units)	December 15, 1955	March 2019 – May 2019 Revision Bulletin

Table 3 – USP Chapters for Insulin

USP Chapter for Insulin	Reference Standard	Date of Admission of First Standard	Date of Most Recent Revision
<121> Insulin Assays	Insulin Glargine (15.06 mg) Insulin Lispro (5.73 mg) Insulin (Beef) (50 mg) Insulin Human (100 mg) Dextrose (500 mg) Insulin Pork (50 mg)	April 19, 2002 1970 (first official date)	March 2019 – May 2019 Bulletin Revision
<121.1> Physicochemical Analytical Procedures for Insulins	None	August 1, 2014	March 21, 2016

Mandatory Public Drug Quality Standards Increase Access to Biosimilars in Europe

Mandatory Public Drug Quality Standards Increase Access to Biosimilars in Europe

JUNE 5, 2019 WASHINGTON, DC

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 fifty 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, nineteen biosimilar products have been approved and eight have been launched.

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 **51 biosimilars (those that were approved in Europe and not later withdrawn – see table on page 4) refer to the manufacturer's use of European Pharmacopeia (EP) 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 USPs). 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 (prev. 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
Amgevita	adalimumab	Amgen Europe B.V.	21/03/2017
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
Blitzima	rituximab	Celltrion Healthcare Hungary Kft.	13/07/2017
Epoetin Alfa Hexal	epoetin alfa	Hexal AG	28/08/2007
Erelzi	etanercept	Sandoz GmbH	23/06/2017
Filgrastim Hexal	filgrastim	Hexal AG	06/02/2009
Flixabi	infliximab	Samsung Bioepis	26/05/2016
Fulphila	pegfilgrastim	Mylan S.A.S	20/11/2018
Grastofil	filgrastim	Apotex Europe BV	18/10/2013
Halimatoz	adalimumab	Sandoz GmbH	26/07/2018
Hefiya	adalimumab	Sandoz GmbH	26/07/2018
Herzuma	trastuzumab	Celltrion Healthcare Hungary Kft.	08/02/2018
Hulio	adalimumab	Mylan S.A.S.	16/09/2018
Hyrimoz	adalimumab	Sandoz GmbH	26/07/2018
Imraldi	adalimumab	Samsung Bioepis NL B.V.	24/08/2017
Inflectra	infliximab	Hospira UK Limited	10/09/2013
Inhixa	enoxaparin sodium	Techdow Europe AB	15/09/2016
Insulin lispro Sanofi	insulin lispro	Sanofi	18/07/2017
Kanjinti	trastuzumab	Amgen Europe B.V., Breda	16/05/2018
Movymia	teriparatide	STADA Arzneimittel	11/01/2017
Mvasi	bevacizumab	Amgen Europe B.V.	14/01/2018
Nivestim	filgrastim	Hospira UK Ltd	08/06/2010
Ogivri	trastuzumab	Mylan S.A.S	12/12/2018
Omnitrope	somatropin	Sandoz GmbH	12/04/2006
Ontruzant	trastuzumab	Samsung Bioepis NL B.V	15/11/2017
Ovaleap	follitropin alfa	Teva Pharma B.V.	27/09/2013
Pelgraz	pegfilgrastim	Accord Healthcare S.L.U	21/09/2018
Pelmeg	pegfilgrastim	Cinfa Biotech S.L.	20/11/2018
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
Ritemvia	rituximab	Celltrion Healthcare Hungary Kft.	13/07/2017
Rituzena (prev. Tuxella)	rituximab	Celltrion Healthcare Hungary Kft.	13/07/2017
Rixathon	rituximab	Sandoz GmbH	15/06/2017
Riximyo	rituximab	Sandoz GmbH	15/06/2017
Semglee	insulin glargine	Mylan S.A.S	23/03/2018
Silapo	epoetin zeta	Stada Arzneimittel AG	18/12/2007
Terrosa	teriparatide	Gedeon Richter	04/01/2017
Tevagrastim	filgrastim	Teva GmbH	15/09/2008
Thorinane	enoxaparin sodium	Pharmathen S.A.	15/09/2016
Trazimera	trastuzumab	Pfizer Europe MA EEIG	26/07/2018
Truxima	rituximab	Celltrion Healthcare Hungary Kft.	17/02/2017
Udenyca	pegfilgrastim	ERA Consulting GmbH	20/09/2018
Zarzio	filgrastim	Sandoz GmbH	06/02/2009
Zessly	infliximab	Sandoz GmbH	18/05/2018
Ziextenzo	pegfilgrastim	Sandoz GmbH	22/11/2018

Endnotes

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: https://www.who.int//biologicals/BiologicalstandardsQAfinal.pdf (accessed May 29 2019).

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 May 29 2019).

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 May 29 2019).

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 May 29 2019); 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 May 29 2019).

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 May 29 2019).

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 May 29 2019).

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 May 29 2019); 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 May 29 2019), ("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," Pharmaceutical Technology 39 (5) May 2, 2015, available at: http://www.pharmtech.com/ensuring-quality-biologicals (accessed May 29 2019).

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 May 29 2019).

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 29 2019).

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 May 29 2019); 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 May 29 2019); 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

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 May 29 2019) ("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 29 2019).

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.long (accessed May 29 2019).

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 May 29 2019).

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 May 29 2019).

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 May 29 2019) 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 May 29 2019); 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 May 29 2019).

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 May 29 2019).

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 May 29 2019).

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 May 29 2019), ("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 and scrutinised to ensure they meet the appropriate stringent criteria of stability, homogeneity and uncertainty. They provide an independent 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 May 29 2019), ("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 May 29 2019).