Commentary

Role of Public Standards in the Safety and Efficacy of Biologic Medicines

Roger L. Williams,¹ Adrian F. Bristow,² Walter W. Hauck,^{1,3} V. Srinivasan,¹ Tina Morris,¹ Fouad Atouf,¹ Michael Ambrose,¹ Koduru V. Surendranath,¹ Ranjan Chakrabarty,¹ and Krishna Menon¹

Received 2 January 2014; accepted 5 March 2014; published online 2 April 2014

Abstract. In this report, we emphasize the importance of public monographs with reference materials, coupled with careful process and change control and attention to GMPs, as a means of advancing access to good quality, safe, and effective medicines, with emphasis on available and incoming biologic medicines. With adequate control of articles covered by a monograph, these public standards can form the basis for a global public quality platform that covers reference products, non-interchangeable reference products, biosimilars, and interchangeable biosimilars. Working collaboratively with all stakeholders, new approaches allow these public standards to emerge nationally and globally in a timely way. Yet, there are increasing limitations in the availability of public standards for biologic medicines, which may reverse many decades of progress. Solutions are considered in this report.

KEY WORDS: biologics; medicine compendium; monographs; reference standards; US pharmacopeia.

INTRODUCTION

Biologic medicines are an increasing component of the therapeutic armamentarium of practitioners, with a long and distinguished history of value to patients/consumers. The increase in the medicinal value of biologics is expected to expand with improved understanding of human and animal biology and rising capability of manufacturers to make safe, effective, and good quality biologics through recombinant technology. Equally important, global, regional, and national approaches to first-entry reference products, other reference products with the same active moiety but without comparison to the first (referred in this article as a non-interchangeable reference products), biosimilars, and interchangeable biosimilars, with the understanding that a global ingredient and product quality platform can be developed that is suitable for all four categories (Fig. 1). We argue that a key component of this platform is a public monograph with allied reference materials that, for potency, are traceable to a World Health Organization (WHO) biological reference material (BRM), denoted as a WHO international standard or reference reagent (1). This report follows a larger paper published by the US Pharmacopeial Convention (USP) that considered primary and secondary standards, together with monographs, for food and drug articles (2).

LIMITATIONS ON AVAILABILITY OF BIOLOGIC PUBLIC STANDARDS

Historically, WHO provides both written and measurement standards for biological medicines, e.g., vaccines and therapeutic proteins. To perform this function, WHO works with various collaborating centers, including the UK's National Institute for Biologic Standardization and Control (NIBSC, which recently joined the UK's Medicines and Health Care Products Regulatory Agency) to prepare BRMs that maintain the unitage of both natural source and rDNA biologic medicines (3). These BRMs are critically important to global and national health as a means of assuring consistency in potency over many years of manufacture and during shelf life. The WHO BRM represents a global primary standard to which a national pharmacopeia or similar standard becomes secondary. Tertiary standards may be developed as working standards by pharmaceutical manufacturers. An excellent review notes the importance of unitage for insulin, an archetypal biologic (4). Typically, the potency test forms the core of a public monograph together with additional physicochemical tests. This approach has worked well, with many BRMs available from WHO (5). Advancing BRMs is becoming more challenging for the newest biological medicines, such as monoclonal antibodies, fusion proteins, and other highly engineered biologics, as there generally is no readily available donor other than a first-entry manufacturer. These molecules, some of which are bioengineered versions of earlier molecules, do not exist in nature, unlike the case for earlier proteins such as insulin, somatotropin, and erythropoietin. However, with the development of multi-source products for the same active moiety, there is an urgent need for standards for monoclonal antibodies and bioengineered molecules (1). The availability of public monographs with reference materials similarly may be constrained.

¹ United States Pharmacopeial Convention, 12601 Twinbrook Parkway, Rockville, Maryland 20852, USA.

² National Institute for Biological Standards and Control, Blanche Lane, South Mimms, Potters Bar, Hertfordshire EN6, 3QG, UK.

³ To whom correspondence should be addressed. (e-mail: wh@usp.org)

Fig. 1. Four categories are emerging globally for a biologic product: (1) reference product, (2) one or more non-interchangeable reference products, (3) one or more biosimilar products to each reference product, and (4) interchangeable biosimilar reference products (USA only). All can be linked via common unitage traceable to an available WHO biological reference material with specified unitage. For categories 1 and 2, clinical trial designs might be based either on demonstrating a difference (two-sided) or non-inferiority (one-sided). For categories 3 and 4, designs are based on demonstrating similarity with criteria for population or individual equivalence. The dark shaded area in the figure denotes varying degrees of intellectual property protection via either patent or exclusivity, ranging from none to a minimum of 12 years exclusivity in the USA via BPCIA

USP typically relies on donation of information and materials for monographs in the US Pharmacopeia-National Formulary (USP-NF) and of allied reference materials, which are made available as USP Reference Standards. While USP often can prepare a monograph with reference materials for chemical medicines independently, this may be more difficult for biologic medicines (6). An interesting case, where USP has a potency test for a biologic medicine in a general chapter but does not have the public monograph, is described in Case Study 1 in Appendix section. While manufacturers may be reluctant to donate because of their desire to protect intellectual property (IP), the need for public standards should not be conflated with the need for IP or exclusivity protection, which is a separate matter subject to national jurisdiction (see Fig. 1). Pharmacopeias do not make medicines and do not engage in market access decisions. Indeed, a strong argument for sound, relevant, timely monographs is that they protect all manufacturers, including those with heavy IP investments, from substandard and falsified medicines (2, 6).

Regulatory approaches to biologics also may limit the availability of public standards. The widespread acceptance of the paradigm that biologics can be adequately controlled through a combination of knowledge of the manufacturing process, clinical data, and the private specification appears to have limited US regulators' support for the added value of separate stand-alone public quality standards for biologics. This approach stands in contrast to that in Europe where regulatory and pharmacopeial experts working in the Council of Europe's European Pharmacopeial Commission, with secretariat support by the EDQM in Strasbourg, emphasize the importance of public standards for biologic medicines in the *European Pharmacopeia* (7).

More recently, the US Biologics Price Competition and Innovation Act (BPCIA), enacted by Congress and signed into law by the president in March 2010, may have advanced

somewhat the possibility of public monographs and reference materials for biologics in USP (8). Some biologic reference product manufacturers may donate information and materials to support a public monograph in the expectation that the resulting USP monograph will create a *de minimus* compendial quality requirement for subsequent competitors. For most biologics, however, licensing/market approval remains an activity carried out in the USA without emphasis on the need for public standards. At this time, of about 400 biotherapeutic agents in the USA, only about 150 have monographs in USP, and about 30% of these need updating.

A GENERAL APPROACH: THE USP MEDICINES COMPENDIUM

Monographs in USP-NF are almost entirely devoted to medicines and medicinal ingredients legally marketed in the USA. In July 2011, USP made available the USP Medicines Compendium (MC). USP's MC provides public standards authorized by the USP Council of Experts for biologic and other medicines legally marketed outside the USA (9). USP uses the term "authorized" to indicate absence of legal recognition, for which the term "official" is sometimes applied. After approximately 30 months of existence, it became apparent that MC approaches, which rely on broadly applicable reference (formerly termed "default") procedures (10), also created opportunities to advance sound monographs with allied reference materials for USP-NF for chemical medicines (6). Monographs for biologic medicines in the MC are concluded by a Biologics Expert Committee of the Council of Experts. The approach of the MC for biologic medicines is based conceptually on a public-private partnership. The public part is USP with interested governmental representatives invited as well (e.g., Korea), while the private part occurs through participation from interested manufacturers. Members from the Biologics Expert

Committee can supply information and materials as they wish, which is then taken up for further research and development work by USP laboratories. Non-industry members support good discussions with all participating in accordance with USP's conflict of interest rules, which require Expert Committee members to withdraw from a concluding deliberation and not ballot if they have a commercial interest in the emerging standard. Based on this *noncompetitive* collaboration, the final authorized monograph with validation data appears on USP's web site and is freely available (11, 12). The noncompetitive character of the effort allows biologic manufacturers to share information and material only as they wish, with USP's laboratories conducting the needed research and development efforts for the public standard. Financing for the effort at this time relies on sale of reference materials as USP Reference Standards. While the MC is not legally recognized per se, its monographs may be used by manufacturers in advancing their private specifications. Further, regulatory agencies may recognize an MC monograph and find value in the secondary authoritative standards that would not otherwise be available. The MC may have additional uses that can evolve over time, particularly given the paucity of official standards for many biologic medicines.

A key part of the work of the Biologics Expert Committee is executed as part of a Memorandum of Understanding between USP and the NIBSC. Via this work, which allows development of USP Reference Standards to support biologics monograph in the MC, there is also a possibility of developing a BRM suitable for consideration by the WHO. The general approach is exemplified in Case Study 2 in [Appendix](#) section for pegfilgrastim.

HORIZONTAL STANDARDS: USP'S GENERAL CHAPTERS

USP intends to keep working on biologic monographs in USP-NF for the USA, which reflects its time-honored work recognized in the Federal Food, Drug, and Cosmetic Act (FDCA) by Congress in 1906 and again in 1938, and applicable as well to biologics approved under the Public Health Service Act. Even if public monographs in USP-NF for specific biologic medicines prove difficult to develop, USP can advance general chapters, termed horizontal standards, in support of private and public specifications (Fig. 2). Particularly, important in the suite of general chapters in the USP-NF are those used to determine potency of a biologic medicine: <111>, <1,030>, <1,032>, <1,033>, and <1,034> (13). USP has agreed to work with NIBSC and other governmental laboratories to assure that the unitage of its biologic reference materials (national official secondary standards of USP-NF in the USA and global authoritative secondary standards in the MC) accords appropriately with WHO BRMs.

CLINICAL STANDARDS

Figure 1 exemplifies the need for a common quality standard to undergird similar biologic medicines. Beyond this need lies an additional set of standards that are used to assess, for purposes of market access, the quality, safety, and efficacy of a biologic medicine for registration purposes. For a first-entry biologic (approved under PHS Act 351(a)), termed the reference product in BPCIA, these studies may involve analytical, preclinical, and clinical investigations (14). The

general approach is also applicable for non-interchangeable copy products. Clinical studies to document biosimilarity, following the scientific logic of BPCIA, would be expected to follow population equivalence approaches (15, 16). Documentation of interchangeability for a biologic medicine shown to be biosimilar to a reference product would be expected to follow an individual equivalence approach (15, 16). In some ways, BPCIA clearly articulates, and to some extent resolves, some of the deficiencies of its predicate law, popularly termed Waxman-Hatch (Drug Price Competition and Patent Term Restoration Act), where regulation still relies on population approaches to document interchangeability, on the assumption that subject-by-formulation interactions do not exist. This assumption is not often tested, and examples exist where it is not true (17). Other science deficiencies in implementation of both Waxman-Hatch and BPCIA remain, e.g., issues of transitivity associated with switching between two biosimilars to a common reference product.

NOMENCLATURE AND THE PUBLIC MONOGRAPH

An important aspect of a public monograph relates to the name of the medicine ingredient or product, which in the case of drugs, including biologics, recognized in USP-NF (i.e., covered by the identity test of a particular monograph) is the title of the monograph (18). The naming of biologic medicines is important for practitioner and patient use and relates specifically to an understanding of identity, as established in the identification test of the private or public specification (19). In the USA, active ingredient (drug substance) names usually come initially from US Adopted Names (USAN) (20), while the Nomenclature, Safety, and Labeling Expert Committee in the USP Council of Experts has the ultimate authority, both under USP rules and under federal law, to designate non-proprietary names for both drug substances and drug products at the time a monograph is approved. This role is explicitly described in the adulteration and misbranding provisions of the US FDCA at Sections 501 and 502. It can be overridden by FDA by notice and comment rule-making under FDCA Section 508, although FDA has never done so (21). USP's role is attenuated if a monograph is absent or if it comes many years after marketing, when a name, termed an interim non-proprietary name, is designated by FDA in a manufacturer-specific application and becomes commonly used, unless and until a different name is later designated in an applicable USP monograph.

BPCIA allows the possibility of several names for the four categories of biologic products now allowed in the US market (Fig. 3). Historically, for the first two (reference product and one or more non-interchangeable reference products), the USA has allowed the same name (e.g., the somatotropins), although there may be a move away from this approach (e.g., TBO-filgrastim for a non-interchangeable reference product to filgrastim (22)). A different name has also been proposed for a biosimilar product to a reference product, ostensibly for purposes of pharmacovigilance. Again, this would be a break from past practice where understanding of interchangeability for drugs approved under the FDCA typically comes from FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (also termed informally the Orange Book) (23) and not via its name, and approaches other than assigning different non-proprietary names

Fig. 2. General chapters in the pharmacopeia, sometimes termed horizontal standards, can support public or private specifications for non-interchangeable biologic reference products and/or for biosimilars

have been relied on for tracking products for pharmacovigilance purposes. Yet, USP’s naming function might allow a compromise as a variation of USP’s current monograph-naming policy (24). Specifically, the biologic ingredient (drug substance) monograph in USP could allow different USAN (providing a test was available to distinguish between the so-named ingredients to provide a basis for a separate drug substance monograph), but the biologic drug product name would use a common name if the drug product monograph identity test covered both products. The approach could be allied with some kind of public notice, similar to the Orange Book, which would provide timely updates as to FDA’s decision-making for the categories denoted in Fig. 1. As noted in the previous section of this commentary, a finding of biosimilarity under provisions of the BPCIA is based on a population, not individual understanding, so involvement of dispensing practitioners might well be needed in changing a patient from a reference product to a biosimilar product. With further documentation and regulatory approval, an interchangeable biosimilar medicine could be substituted without involving the dispensing practitioner. One solution to the general set of BPCIA naming challenges might be to prescribe biologics by brand names to signal a change to practitioners unless interchangeability was confirmed. In any event, having specific and separate non-proprietary names for all

possible categories of biologics shown in Fig. 1 seems difficult (Fig. 3), and the need for this approach on pharmacovigilance or other grounds is perhaps not well supported by data.

SUMMARY

Public standards for all medicines, including biologic medicines, are critically important to all stakeholders—and particularly the public at large. The need for a common quality standard to assure the quality of biologic medicines moving in national and global commerce is important. Public-private partnerships, working at times noncompetitively, may resolve barriers to availability of public standards. Barring an ability to control a biologic medicine in the marketplace through physicochemical tests alone, a biologic medicine will require one or more potency tests to assure its quality during its time in the market. Careful adherence to other application commitments, GMPs, change control, and good supply chain management to the point of practitioner use is equally critical. Naming of a biologic medicine should be kept simple and consistent with longstanding compendial naming conventions to aid in practitioner and patient use, with clear public notification, to indicate whether it is the following: (a) non-interchangeable, (b) biosimilar, or (c) both biosimilar and interchangeable to a predicate reference product. In the absence of interchangeability, the use of brand names for prescribing biosimilars approved on the basis of population-based clinical studies seems logical.

APPENDIX

Case Studies

Case Study 1: USP’s Erythropoietin Bioassay Reference Standard

Epoetin alpha is the USAN of a drug substance that is marketed in the USA as epoetin alpha for injection by

Fig. 3. Assuming one reference product (RP), one follow-on non-interchangeable reference product (NI-RP), and two biosimilars for each, coupled with a further decision of interchangeability for each, a name might signal up to 10 regulatory decisions, e.g., 1 [NAME]-RP1; 2 [NAME]-RP2 (non-interchangeable); 3, 4 [NAME]-BS1 and [NAME]-BS2 to RP1; 5,6 [NAME]-BS1 and [NAME]-BS2 to RP2; and 7, 8, 9,10 signal interchangeability for each biosimilar

Amgen for general anemia beginning in 1989 and by Johnson and Johnson for anemias of cancer also beginning in 1989. USAN has given two additional names for erythropoietin (EPO): beta and delta, even though only the *alpha* form is marketed in the USA. The *beta* form is marketed in Europe as NeoRecormon by Roche. The WHO has created three EPO international standards (IS) in 1990, 2003, and 2012, respectively. The second IS was composed of a mixture of the alpha and beta forms. There is no indication that the alpha and beta forms produce different clinical effects, and the two different forms can only be distinguished with high resolution charge separations or glycan analysis that can address glycosylation microheterogeneity. In the absence of a monograph for erythropoietin, USP's Biologics & Biotechnology Monographs 1 Expert Committee prepared general chapter *Erythropoietin Bioassay* <124> (25) that provides procedures for two *in vivo* animal assays, one in normocytic mice and one in polycythemic mice. It also provides further guidance on how an *in vitro* bioassay might be calibrated relative to the *in vivo* assays. The candidate reference material for this general chapter is the same material as the recently established third international reference standard (RS) for erythropoietin (WHO's BRM). USP's laboratories did not participate in this collaborative study, but the results from the WHO collaborative study were used to establish USP's EPO potency standard in general chapter <124> with the same unit assignment as the WHO third IS. Additional studies will be needed to develop a reference material for the physicochemical tests of the planned epoetin alpha drug substance monograph in USP. The third IS for erythropoietin is no longer a mixture of alpha and beta erythropoietin but contains only epoetin alpha, and the third IS is the same material referenced in general chapter <124>, even though the USP material is considered a secondary national reference material.

Use of the USP Reference Standard in the Context of In Vitro Bioassays

The USP erythropoietin (EPO) for bioassay reference standard (RS) is directly traceable to the third WHO international standard for EPO which is calibrated by *in vivo* bioassay in IU. Transfer of the unitage (IU) from the USP potency standard to any process-specific EPO material, where that material has the potential to differ in its ratio of biological activities from the USP potency standard, must be made with a full understanding of the biological properties of the material.

The USP EPO for bioassay RS is assigned a unitage of 1,500 units/IU by *in vivo* assay. The USP potency standard may be used directly in the normocytic mouse bioassay, as described in chapter <124>, and for the calibration of any process-specific EPO preparation. However, if the intention is to use an *in vitro* assay and to transfer the unitage from the USP EPO for bioassay RS to a preparation of EPO, then it is necessary to demonstrate that the USP potency standard and the material in question exhibit equivalent ratios of *in vitro* to *in vivo* potency (25). When these ratios are not equivalent, then the standard may not be used with its assigned *in vivo* potency in the *in vitro* assay, and the ratio determined for the material being tested should then be used to assign a process-

specific, *in vitro* assay unitage to the USP EPO for bioassay RS. The USP EPO for bioassay RS, with its adjusted *in vitro* assay unitage, may then be used in the *in vitro* assay to transfer the unitage from the USP EPO for bioassay RS to the material being tested.

Case Study 2: Pegfilgrastim (PEG-G-CSF) Potency Test and Reference Materials

Filgrastim (G-CSF) binds to high-affinity G-CSF receptors and regulates the maturation and proliferation of neutrophils within the bone marrow. Therapeutically, the drug is used to reduce the neutropenic phase arising from certain disorders or as a result of cancer chemotherapy. Pegfilgrastim (Peg-G-CSF) is a mono-pegylated form of the recombinant human granulocyte colony-stimulating factor analog, filgrastim. It is a single chain, 175 amino acid, pegylated polypeptide. It is prepared by coupling a linear polyethylene glycol (PEG) molecule, of an average molecular weight of 20 kDa, to the N-terminus of the filgrastim protein. The change decreases renal clearance and allows reduction in the frequency of dosing. The drug has been marketed in the USA and in Europe under the brand name Neulasta by Amgen since 2002 and has recently been one of the most notable targets for the development of both non-interchangeable and biosimilar products. Products have already been launched in Europe (Teva) or are in late clinical development (Sandoz), demonstrating that the time is right for the development of a public standard that can reconcile key quality expectations for the global market.

The PEG-G-CSF drug substance monograph for USP's Medicines Compendium (MC) was developed in USP India Private Limited Laboratories in Hyderabad, in consultation with the Council of Experts MC Biologics Expert Committee. Critical quality attributes for the tests, procedures, and acceptance criteria of the monograph were determined. Candidate procedures were validated using donated materials from six manufacturers and a reference product, Neulasta, procured from the Indian market. The potency test for the MC monograph is based on a cell proliferation assay with read-out expressed in fluorescence. In parallel with USP's effort, the NIBSC conducted a global collaborative study to develop the WHO first IS for *in vitro* bioactivity of PEG-G-CSF in medicinal products or their ingredients. Three manufacturers donated material to NIBSC for this study. Two materials were lyophilized as per WHO specifications, and the study was conducted in the following laboratories: four from China (including the National Institute for Food and Drug Control in Beijing), four from Europe (including NIBSC), eight from India (including the National Institute for Biologics near Delhi and USP facilities in Hyderabad and Rockville), two from South Korea, three from Latin America, and USP's laboratories in Rockville. For the first time, two USP laboratories have participated in an international study for the establishment of an IS for a recombinant therapy. Based on the results of the collaborative study, NIBSC has prepared 4,700 ampules at 1 µg/mL with a value assignment of 10,000 IU/ampule. NIBSC submitted a report to the World Health Organization's Expert Committee on Biological Standardization at their October 2013 meeting and thereafter

made the first IS for a PEG-G-CSF BRM available to the global community. Since the standard has only been evaluated for use in an *in vitro* bioassay, it cannot be assumed to be suitable for evaluation *in vivo* or for pharmacokinetic studies or for other purposes without suitable validation.

Typically, WHO's BRM materials are provided only in small amounts for calibration of national primary and manufacturer secondary standards. The material is not intended for batch release testing. Because the candidate reference material for the USP MC potency test was also assessed in the NIBSC collaborative study, this material may be used throughout the world for batch release testing, using the potency test procedures described in the USP MC monograph or in any other procedure where unitage is linked to the WHO first IS PEG-G-CSF BRM. With availability of the first IS from WHO for PEG-G-CSF for potency testing, national primary and industry second standards should be recalibrated to this material to assure consistency in unitage across all PEG-G-CSF medicinal products where possible.

USP is also developing a physicochemical RS for pegfilgrastim to support the MC monograph. This will be a qualitative RS designed to (1) identify peaks/bands, (2) match peaks/bands for purpose of identification and detection, (3) match peptide map profiles, (4) evaluate and resolve chromatography peaks, and (5) demonstrate method performance. The RS will not be used to assign a value (potency or purity), although it will have an assigned concentration for purposes of sample dilution. Collaborative testing will include USP India, USP Rockville, NIBSC, and manufacturers from India and abroad.

REFERENCES

1. Wadhwa M, Thorpe R. European perspective on biosimilars. *Bioanalysis*. 2013;5(5):521–4. doi:10.4155/bio.13.2.
2. Hauck WW. USP Council of Experts, USP Standards Committee. Primary and secondary reference materials for procedures to test the quality of medicines and foods. *Pharm Res*. 2012;29(4):922–31.
3. NIBSC. http://www.nibsc.org/products/reference_standards/biological_reference_materials.aspx Accessed 17 Sep 2013.
4. Fields B. From rabbits to the League of Nations: early standardization of the insulin unit. *The Pharos*. 2011;74(1):28–33.
5. WHO. http://www.who.int/biologicals/reference_preparations/en/. Accessed 17 Sep 2013.
6. Williams RL. Public documentary standards and reference materials. *Pharmaceutical Forum*. 39(1). <http://www.usppf.com/pf/pub/index.html> Accessed 17 Sep 2013.
7. EMA Guideline on Bioanalytical Method Validation, 21 July 2011. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf Accessed 11 Dec 2013.
8. Patient Protection and Affordable Care Act, Public Law 111–148 (2010), Title VII, Subtitle A—biologics price competition and innovation, amending the FDCA and Public Health Service Act (adding a new biosimilars approval pathway in subsections (k) and (l) of 42 U.S.C. §262, Regulation of Biological Products).
9. USP. *Medicines Compendium*. <https://mc.usp.org/homepage?destination=homepage>. Accessed 17 Sep 2013.
10. Small Molecules Collaborative Group, William RL, Abernethy DR, Koch WF, Hauck WW, and Cecil TL. Performance-based monographs. *Pharmaceutical Forum* 35(3) <http://www.usppf.com/pf/pub/index.html> Accessed 3 Dec 2013.
11. Biologics and biotechnology manufacturers. <http://www.usp.org/usp-manufacturers/biologics-biotechnology> Accessed 17 Sep 2013.
12. USP Rituximab Monograph, *Medicines Compendium* <https://mc.usp.org/monographs/rituximab-1-0> Accessed 9 December 2013.
13. USP. USP-NF. <http://www.usp.org/usp-nf>. Accessed 17 Sep 2013.
14. FDA. Title VII—improving access to innovative medical therapies. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf> Accessed 17 Sep 2013.
15. FDA. Guidance for industry. Statistical approaches for establishing bioequivalence. <http://www.fda.gov/downloads/Drugs/Guidances/ucm070244.pdf>. Accessed 17 Sep 2013.
16. Hauck WW, Anderson S. Types of bioequivalence and related statistical considerations. *Int J Clin Pharmacol Ther Toxicol*. 1992;30:181–7.
17. Hauck WW, Hyslop T, Chen ML, Patnaik R, Williams RL. Subject-by-formulation interaction in bioequivalence: conceptual and statistical issues. FDA Population/Individual Bioequivalence Working Group. Food and Drug Administration. *Pharm Res*. 2000;17(4):375–80.
18. “Draft guidances related to the development of biosimilar products; public hearing; request for comments,” 77 *Federal Register* 42 (2 March 2012), pp 12853–12855.
19. USP-NF General Notices, Section 5.40, “Identity.”
20. USP. USP Dictionary of United States Adopted Names (USAN). <http://www.usp.org/store/products-services/usp-dictionary> Accessed 17 Sep 2013.
21. USP. Compendial nomenclature. <http://www.usp.org/usp-nf/development-process/compendial-nomenclature> Accessed 17 Sep 2013.
22. WHO. 55th Consultation on International Nonproprietary Names for Pharmaceutical Substances Geneva, 16–18 October 2012. https://healthpolicynewsstand.com/iwfile.html?file=mar2013%2Fhe2013_0218.pdf. Accessed 17 Sep 2013.
23. FDA. Orange Book: approved drug products with therapeutic equivalence <http://www.accessdata.fda.gov/Scripts/cder/ob/default.cfm> Accessed 2 Dec 2013.
24. USP. Monograph naming policy. <http://www.usp.org/usp-nf/development-process/compendial-nomenclature/monograph-naming-policy> Accessed 17 Sep 2013.
25. USP. <124> Erythropoietin bioassays. *Pharmaceutical Forum*. 39(5). <http://www.usppf.com/pf/pub/index.html>. Accessed 31 Jan 2014.