Draft FDA Guidance “Considerations in Demonstrating Interchangeability with a Reference Product”: Overview and Presentation-Related Concerns

In mid-January, the U.S. Food and Drug Administration (FDA) released a draft Guidance for Industry regarding demonstration of interchangeability with a reference product.¹ Two excellent summaries were published by the law firms of Ropes & Gray and Latham & Watkins.^{2,3} The deadline for receipt of comments is March 20, 2017.⁴

The Biologics Price Competition and Innovation Act (BPCIA) stipulates that product sponsors must demonstrate that a biological product is biosimilar to the reference product.⁵ For the interchangeability designation, a sponsor must demonstrate that if the product is “administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.”⁶

The FDA guidance stipulates that a sponsor of an interchangeable product generally should not seek licensure for a presentation for which the reference product is not licensed and provides, for example, that if a reference product is only marketed in a vial and a prefilled syringe, a sponsor should not seek licensure for the proposed interchangeable product in a different presentation, such as an auto-injector.

Differences in presentation between proposed interchangeable and reference products may be acceptable if design differences do not increase error risks for patient and caregiver end-user groups. This is necessary to ensure appropriate use when the interchangeable product is substituted for the reference product without intervention of the prescribing health care provider or the provision of additional training before use.

This draft guidance raises the following concerns:

1. Might the FDA designate only some of a marketed biosimilar’s presentations (e.g., the container closure system or delivery device) as “interchangeable,” leaving others as originally approved? How will prescriptions, labeling, formularies, the Healthcare Common Procedure Coding System, and Medicare biosimilar modifier coding make this distinction clear, understandable, implementable (by the pharmacy), and trackable?
2. A reference product’s delivery device is patented. The delivery device of the proposed interchangeable must be sufficiently different to avoid patent infringement. The FDA guidance stipulates that an interchangeable product cannot require additional instruction to ensure proper administration. How can these constraints be reconciled?
3. The guidance strongly discourages a proposed interchangeable product submission using a delivery device not approved for the reference product, and differences in design of the container closure system or delivery device must not increase end users’ administration error rate. Are these meaningful distinctions?

4. Consider a biosimilar whose delivery system is unlike that of the reference product and can demonstrate lower user error rate or increased adherence—clearly a patient benefit. Why is this biosimilar presentation ineligible for interchangeable designation, as the guidance suggests?
5. The Biologics Price Competition and Innovation Act stipulated pharmacist substitution of interchangeable products without prescriber intervention. Several states have passed laws restricting the circumstances of and defining operational aspects of this process.⁷ Might variability in biosimilar presentation, sometimes designated as interchangeable for some or all of a reference product’s labeled indications, complicate pharmacist consideration of product comparability?

Elan Rubinstein, PharmD, MPH

EB Rubinstein Associates

elan.b.rubinstein@gmail.com

DISCLOSURES

Rubinstein provides consulting services to the pharmaceutical industry, health plans, employers, and specialty pharmacies, and is a member of the editorial advisory board of *Specialty Pharmacy News*. He was a participant on the Amgen Biosimilar Report Advisory Board and reports consulting fees from Amgen.

REFERENCES

1. U.S. Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product. Guidance for industry. Draft guidance. January 2017. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf>. Accessed February 9, 2017.
2. Ropes & Gray. FDA issues draft guidance on biosimilar interchangeability. FDA regulatory alert. January 27, 2017. Available at: <https://www.ropesgray.com/newsroom/alerts/2017/01/FDA-Issues-Draft-Guidance-on-Biosimilar-Interchangeability.aspx>. Accessed February 9, 2017.
3. Latham & Watkins. FDA issues draft guidance on biosimilar interchangeability. Client Alert Commentary. January 27, 2017. Available at: <https://www.lw.com/thoughtLeadership/LW-FDA-issues-guidance-on-biosimilar-interchangeability>. Accessed February 9, 2017.
4. Submit electronic comments at: <https://www.regulations.gov>. Reference name of draft guidance and Docket No. FDA-2017-D-0154.
5. U.S. Food and Drug Administration. Information on biosimilars. Updated May 10, 2016. Available at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars>. Accessed February 9, 2017.
6. Biologics Price Competition and Innovation Act. Title VII, Subtitle A, Sec. 7001-7003. H.R. 3590. The Patient Protection and Affordable Care Act. 2009. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf>. Accessed February 9, 2017.
7. Cauchi R. State laws and legislation related to biologic medications and substitution of biosimilars. National Conference of State Legislatures. November 15, 2016. Available at: <http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx>. Accessed February 9, 2017.