BakerHostetler

BRIEF

Innovator Company Advocacy for Heightened ANDA Approval Standards – Complex Drugs

Lance L. Shea, M.S., J.D. and Lorin K. Johnson, Ph.D.

In its eighth annual report,[1] the FDA's Office of Generic Drugs (OGD) made clear that "generic drugs remained a significant public health priority for the FDA." OGD is pursuing several important initiatives to foster the approval of complex generic drugs. "The GDUFA Science and Research Program is particularly important for . . . complex products, which are harder to develop as generics."[2] "The implementation of GDUFA III . . . brings the generic drug program to yet another level . . . enabl[ing] further regulatory science research around complex and other generic drug development."[3] The FDA is directly enabling generic sponsors: "GDUFA research outcomes also allowed FDA to . . . provide prospective ANDA applicants with scientific and technical advice that helped them prepare submissions consistent with FDA's most current scientific thinking and regulatory requirements. In 2022, FDA facilitated 108 such product development and pre-submission pre-ANDA meetings."[4] Further, the FDA "conducted 13 workshops and webinars for [the generic] industry . . . ."[5]

Generally, the OGD's efforts are in accordance with Congress' mandate to spur development of generic drugs. Yet, we have seen instances in which the OGD has proposed recommendations for generic approval standards that have not been sufficiently rigorous. Those instances have involved complex reference listed drugs (RLDs) – products such as those that act locally, have multiple active ingredients, or have active delivery systems composed of what previously may have only been considered "inactive ingredients."

The purpose of this white paper is to describe our approach to engaging the OGD with the purpose of ensuring that approval standards for generic versions of complex RLDs are sufficiently rigorous. Below, we introduce two key concepts: bioequivalence of the active principle (BE – Active Principle) and bioavailability mechanism analysis (BA Mechanism Analysis). By employing those concepts, innovator companies can effectively advocate for appropriate approval standards for generic versions of complex RLDs.

KEY POINTS

- **Through its Drug Competition Action Plan, the FDA is engaging heavily with generic drug sponsors to foster approval of complex generic drugs. In October 2022 alone, the FDA issued over 80 product-specific guidances (PSGs) aimed at speeding development of complex generic skin drugs.**
- **In 2023, the FDA issued at least 97 new or revised PSGs aimed at fostering generic products. Over 60% targeted complex drugs.**
- **Despite the FDA's efforts, our experience shows that brand sponsors can have better insight into the appropriate level of ANDA approval standards than the Agency or generic industry.**
- **Brand sponsors can successfully seek improved generic approval standards if they develop compelling evidence to support specific standards and begin advocacy soon after approval of the RLD.**

BE – Active Principle – Framing the Evidence Supporting Appropriate Generic Approval Standards

The term "active principle" is defined as follows:

1. A chemical component.
2. A substance or combination of substances on which certain of the properties of a drug depend.
3. An accepted or professed rule of action or conduct. In a given philosophical system, it is a fundamental or general law or truth from which others are derived. In bioethics, some important principles are beneficence, justice, nonmaleficence and respect for autonomy; these are derived in part from professional roles and traditions.[6]

Applied to the FDA's approval of generic drugs or combination products, active principle is a term with two related meanings. The first pertains to the drug's marketing approval process ("rule of action or

[1] U.S. Food & Drug Administration, Office of Generic Drugs 2022 Annual Report – Ensuring high-quality, affordable generic drugs are available to the American public, 1 (Mar. 1, 2022).
[2] Id. at 2.
[3] Id. at 8.
[4] Id. at 10.
[5] Id. at 11.

[6] https://medical-dictionary.thefreedictionary.com/active+principle.

conduct," definition 3 above – the Active Principle Rule). The second pertains to the drug's physicochemical characteristics ("components and properties," definitions 1 and 2 above – the Active Principle Characteristics). Both meanings are discussed below.

Active Principle Rule. The Active Principle Rule applies to the process by which drugs or combination products are approved for marketing: the foundational rules used by the FDA to approve NDAs or ANDAs. For ANDA approval, the Active Principle Rule requires therapeutic equivalence (TE) of the test to the RLD.

To satisfy that rule, the ANDA sponsor must present substantial evidence of pharmaceutical equivalence (PE) and BE. To be pharmaceutically equivalent to the RLD, the test must contain the same active ingredient (the active ingredient sameness criterion). To be bioequivalent, the test must have bioavailability equivalent to that of the RLD at sites of action (the bioequivalence criterion). Put simply, the Active Principle Rule for ANDA approval can be summarized as follows: The test must be TE to the RLD, where TE = PE + BE.

Active Principle Characteristics. To determine whether the substantial evidence threshold is met for the PE and BE criteria, the second meaning of active principle becomes important: The test drug's ingredient and formulation characteristics must be addressed.

Regarding PE (the active ingredient sameness criterion), having an active ingredient with the same molecular structure may be sufficient for many test drugs. Such is not the case, however, where (1) the RLD's active molecular entity can exist in a product formulation as different physicochemical structures and (2) those different structures have different bioavailability profiles. For such drugs, ANDA sponsors must demonstrate that the test drug's active ingredient's structural features that affect bioavailability are the same as those features of the RLD active ingredient. Thus, the Active Principle Characteristics for a test may go beyond molecular sameness to encompass physicochemical sameness.

Regarding BE (the bioequivalence criterion), having equivalent results from relatively simple in vivo and in vitro studies may be sufficient for many test drugs. For example, some systemically acting tablet products administered orally may be approved on the basis of in vivo blood plasma pharmacokinetic profiles and in vitro dissolution profiles, where those products are rapidly dissolved and absorbed into the systemic circulation.

Such is not the case, however, for drugs that are topically acting, that contain complex active ingredients or that are oral products that have low solubility and low systemic permeability. An example would be a two-active-ingredient drug formulation that was topically acting and had a formulation of inactive ingredients that determined the active ingredients' delivery to sites of action. Another example would be an oral drug that acted topically in the gastrointestinal lumen and had low solubility and systemic permeability. For such test drugs, BE evidence may be needed from clinical endpoint BE studies or requirements that the inactive ingredients be the same as those in the RLD and the formulation have physical properties similar to the RLD. Thus, Active Principle Characteristics for a test formulation will drive the type and extent of BE evidence needed for the BE requirement.

The active principle concept may apply to drug/device combination products as well. Consider a contact lens that delivered ocular drugs through topical application, where properties of the lens material would determine the rate and extent of active ingredient delivery.

Bioavailability Mechanism Analysis – Developing the Evidence Supporting Appropriate Generic Approval Standards

An RLD's mechanism of producing bioavailability (BA Mechanism) determines the RLD's performance characteristics. Analysis of that Mechanism (BA Mechanism Analysis) identifies the evidence needed to prove both PE and BE.

As to the PE criterion, BA Mechanism Analysis of the RLD active ingredient is needed to determine whether that ingredient's physicochemical properties are likely to impact bioavailability at sites of action. If so, evidence of physicochemical active ingredient sameness must be required to prove PE.

As to the BE criterion, BA Mechanism Analysis of the RLD's formulation is needed to determine whether properties of the inactive ingredients impact bioavailability at sites of action, unless direct measurement at the sites of action or surrogate locations can provide that evidence. Where direct measurement is not available, BA Mechanism Analysis of the finished product is essential to determining the evidence that must be presented for ANDA approval.

Thus, BA Mechanism Analysis is crucial to determining whether a proposed generic formulation can be approved as therapeutically equivalent to, and substitutable for, an RLD. Put another way, BA Mechanism Analysis is necessary for developing evidence sufficient to convince the OGD to require appropriately rigorous generic approval standards.

BA Mechanism Analysis Should Be Conducted Early

To be used optimally, BA Mechanism Analysis should be conducted early in the RLD's life cycle. This is true for several reasons.

First, the analysis is conducted most efficiently while the drug development team is together and fully engaged. When we have been engaged near the end of marketing exclusivity, we have found that the development team was no longer together. Members had departed or been reassigned. The knowledge of those remaining had become stale. In those engagements, we have needed to build and educate a new team. The cost and time of doing so could have been avoided if the analysis had been done earlier, with the original development team.

Second, conducting early BA Mechanism Analysis will allow the most effective advocacy for generic approval standards. If submitted to the OGD soon after RLD launch, positions on generic approval

standards will be best timed to affect product-specific guidance recommendations. If the OGD's recommendations miss the mark, the RLD sponsor will be in the best position to seek revisions through comments, meetings or a subsequent citizen petition.

More specifically, the sponsor could: (1) submit comments on the PSG; (2) request a meeting with the FDA to present positions and evidence; (3) submit a citizen petition before it became subject to FDCA Section 505(q); or (4) publish certain aspects of the analysis in peer-reviewed literature (depending on trade secret protection concerns). Where circumstances do not permit earlier engagement of the FDA, the client may submit an evidence-based citizen petition subject to Section 505(q) (depending on when supporting evidence was developed).[7]

BA Mechanism Analysis Can Inform Initial Drug Selection and Formulation Decisions

As discussed above, evidence of therapeutic equivalence is more difficult to develop for RLDs with certain active principles. Examples are RLDs that: (1) act locally rather than systemically; (2) are oral products with poor dissolution and absorption profiles; (3) have complex active ingredients that act in complex ways; (4) have active ingredients that act in accordance with their physicochemical properties rather than merely their molecular configurations; and (5) have inactive ingredient formulations that determine the rate or extent of active ingredient delivery to sites of action. If engaged during initial drug selection and formulation decision-making, BA Mechanism Analysis can help guide those processes toward candidates with potentially longer exclusivity life cycles. Also, such early engagement would aid the development of evidence supporting reliable and appropriately rigorous approval standards for generic versions of the RLDs that are selected for development.

[7] In 2007, Congress enacted Federal Food, Drug, and Cosmetic Act § 505(q) that "applies to certain petitions that request that FDA take any form of action related to a pending ANDA or 505(b)(2) application . . . The Food and Drug Administration Safety and Innovation Act (FDASIA) . . . expanded the scope of section 505(q) to include certain petitions related to 351(k) applications." U.S. FOOD & DRUG ADMIN., Citizen Petitions and Petitions for Stay of action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act – Guidance for Industry 2 (Sept. 2019).

Lance Shea, M.S., J.D., *is a partner at BakerHostetler, Co-Chair of the Firm's FDA Practice Team. His practice is focused on matters that will be decided on the basis of health science evidence, usually evidence developed from efficacy, safety or bioequivalence information. Examples are advising on innovator drug approval standards (rare disease drugs, drugs for end-stage diseases), advocating for appropriate approval standards for generic versions of clients' innovator drugs, and advising on alleged links between clients' products and significant adverse events. In addition to his law practice, Lance is Affiliate Assistant Professor, Pharmaceutical Health Services Research, University of Maryland School of Pharmacy.*

Lorin K. Johnson, Ph.D. *is founder and Chief Scientist of Glycyx PharmaVentures Ltd., a biopharma investment and development company. In 1989, he co-founded Salix Pharmaceuticals, Inc. (Nasdaq: SLXP), a GI specialty pharmaceutical company, and held senior leadership positions prior to its $15.8 billion acquisition by Bausch Health Inc. (NYSE: BHC) in April 2015. Prior to Salix, Dr. Johnson served as Director of Scientific Operations and Chief Scientist at Scios, Inc. (formerly California Biotechnology, Inc). He is a board member of 9Meters Biopharma Inc. (Nasdaq: NMTR) and Edesa Biotech. Inc. (Nasdaq: EDSA), Glycyx MOR, Inc. and Kinisi Therapeutics, Ltd., both GI specialty pharma companies and Intact Therapeutics, Inc., a GI specialty drug delivery company. In addition to his career in industry, Dr. Johnson has served as Assistant Professor of Pathology at Stanford University School of Medicine. He is the co-author of 75 journal articles and book chapters and is the coinventor on 22 issued patents. Dr. Johnson holds a Ph.D. from the University of Southern California and was a Postdoctoral Fellow at the University of California, San Francisco.*

CONTACT

Lance L. Shea M.S., J.D.
Partner
Washington, D.C.
T +1.202.861.1648
lshea@bakerlaw.com