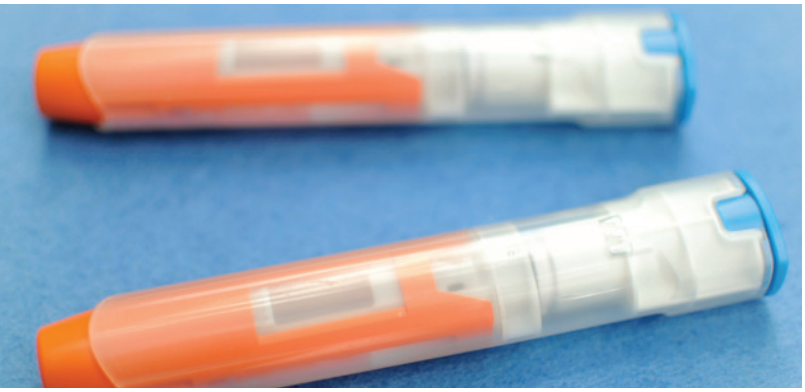
Addressing Barriers to the Development of Complex Generics:

Understanding Challenges and Opportunities

About USP

USP is an independent, nonprofit, science-based organization that helps to safeguard the public's health globally by developing quality standards for medicines, compounded preparations, dietary supplements, food ingredients, and healthcare quality. USP standards are developed through independent experts in a transparent scientific process with input from stakeholders and federal agencies such as the FDA and the CDC.

USP published the first edition of a national, uniform set of guidelines in 1820 for the best understood medicinal substances and preparations of the day. USP standards for drug quality have been recognized in federal law since 1906 and are enforceable by FDA. Additionally, USP standards are recognized in state laws and are enforceable by state regulatory bodies such as Boards of Pharmacy.





What are complex generics?

By definition, generic drugs are "medication(s) created to be the same as an already marketed brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use. These similarities help to demonstrate bioequivalence, meaning that the generic medicine works in the same way and provides the same clinical benefit as the brand name medicine."[1]

As the number of complex brand-name (innovator) products on the market has increased, the scientific and regulatory process and pathways for development and approval of generic versions of these drugs and drug products, commonly referred to as complex generics, may not be as well-established as with innovator drug products.

Complex generics are broadly categorized and typically contain at least one component of the following:

- complex active pharmaceutical ingredients (APIs), such as peptides or complex mixtures;
- complex formulations, such as liposomes or colloids;
- complex routes of delivery, such as dermatological products or otic dosage forms that are formulated as suspensions, emulsions, or gels;
- complex dosage and complex drug-device combination products, such as metered dose inhalers or pre-filled auto-injectors[2], and
- other products "where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement."[3]

Challenges to the development and approval of complex generics

Complex generics represent a smaller share of all approved generics compared to reference listed drugs products, which are the approved products that potential generics are compared to. In Fiscal Year 2022, 13% of the approved generic drugs were classified as complex generics, while complex generics constitute 25% of all approved reference listed drugs available on the market.[4]

Complex generics must meet the same requirements as non-complex generics, but this can be more difficult for manufacturers to demonstrate using traditional methods for a variety of reasons. The manufacturing of these complex products may be difficult due to lack of expertise and equipment, use of complex excipients, lack of methodologies for the analysis and to prove the *in vitro* bioequivalence, etc. In some cases, the therapeutic effect is delivered locally rather than systemically, or the mixture of components contains more than one active molecule.[5] Technical considerations unique to certain complex products, such as complex injectables, drug/device combination products, and topical and transdermal products also create distinct challenges. As a result of these factors and other characteristics, complex generic products are less likely to be available than other generics, face less competition, and are less accessible to patients than non-complex products.

The economic and access cases for fostering development and approval of complex generics

Generic drugs are a vital part of the health care system, offering lower-cost alternatives to brand name products while providing the same clinical benefit for patients. Generic drugs now account for approximately 90% of prescriptions filled in the United States (U.S.), up from 72% ten years ago, and chosen 97% of the time when available. Using data from IQVIA, the Association for Accessible Medicines (AAM) reports that generic and biosimilar drugs saved the U.S. health care system—including patients—about $2.6 trillion in the past decade.[6] In its most recent report, AAM states that generics (excluding biosimilars) saved $366 billion in 2021 alone, of which 32% was saved in Medicare Part D and 16% in Medicaid.[7]

Patients rely on complex drug products for many indications, including chronic and serious conditions such as diabetes, asthma, and cancer. According to the U.S. Centers for Disease Control and Prevention (CDC), one in ten adults in the U.S. has one chronic disease, and four in ten have two or more chronic diseases. For patients with multiple chronic illnesses that require frequent drug refills, the lack of complex generics may be felt acutely. Moreover, the lack of complex generics costs health care systems globally billions of dollars annually.

For example, Matrix Global Advisors studied seven complex generics approved in Canada or Europe but not in the U.S. Their study estimated that the approval of these products in the U.S. would yield annual savings to the healthcare system (including for patients) between $600 million and $1.7 billion.[8]

U.S. government and regulatory efforts to bolster access to complex generics

Promoting a science-based, streamlined, and predictable regulatory pathway and lowering the regulatory barriers for complex generic market entry is a priority for the U.S. Food and Drug Administration (FDA). Through the Office of Generic Drugs (OGD), FDA has undertaken numerous efforts to support the development and accessibility of complex generics by researching the scientific, technological, and regulatory challenges that may affect the development of complex generics.

The Generic Drug User Fee Amendments (GDUFA), first established in 2012, provided funding for FDA to establish a regulatory science program to address scientific challenges that delay access to complex generics. As part of this program, FDA publishes product-specific guidances (PSGs) outlining the Agency's scientific expectations for specific complex generic products. As part of a study on the cost of generic drug development, industry representatives interviewed indicated that the existence of a PSG can save years of development, especially for complex generic drugs.[9] In addition, to enhance and facilitate communication between FDA and sponsors, GDUFA II established a pre-abbreviated new drug application (ANDA) program. This allows for increased communication between FDA and industry prior to ANDA submission, which can help to clarify regulatory expectations, promote efficiency and efficacy in the ANDA process, and reduce the number of review cycles required to obtain ANDA approval, potentially bringing complex generic products to market more quickly.

FDA, industry, and academia have prioritized efforts, through the most recent reauthorization of GDUFA (GDUFA III), to explore various approaches that could resolve outstanding scientific, technical, regulatory, and business practice challenges. Under the GDUFA III commitment letter, FDA has committed to issuing PSGs for complex products approved in new drug applications (NDAs) to generate evidence to support ANDA submissions and approval.[10]

In 2020, FDA awarded grant funding for the establishment of the Center for Research on Complex Generics (CRCG), which supports OGD's efforts to enhance research collaborations, promote training and educational opportunities, and conduct research and technique development related to complex generic products. CRCG has convened a number of workshops and webinars that actively engage participants in trainings and discussions on topics including considerations for bioequivalence studies for generic orally inhaled drug products and best practices for excipient and formulation assessments. Two 2023 CRCG workshops, Identifying, Developing, and Evaluating Generic Drug Device Combination Products, and Mitigation Strategies for Nitrosamine Drug Substance Related Impurities: Quality and Bioequivalence Considerations for Generic Products, addressed practical concerns and challenges faced by generic drug developers.

Collaborative efforts to support complex generic drug development by global regulatory agencies

In light of the increasingly globalized market for pharmaceuticals, enhanced communication and collaboration between regulators is necessary to support the development and availability of complex generics globally. In September 2021, the European Medicines Agency (EMA) and FDA announced the EMA-FDA Parallel Scientific Advice for Hybrid/Complex Generic Products pilot program with the goal of enhanced communication and information sharing from the two agencies to sponsors from the beginning of the product lifecycle. The agencies note that achieving harmonization and increased convergence are potential benefits of the program, however, it is a voluntary program and only available for products where EMA's and FDA's definitions of hybrid products and complex products, respectively, overlap.[11]

In a review of the overall program (not limited to the hybrid/complex generic product program) authored by scientists overseeing the initiative at EMA and FDA, they observed that it is common for discussions to result in convergence of advice.[12]

The FDA also established the Global Generic Drug Cluster, a multi-country forum, "to achieve a common understanding of each member agency's generic drug regulatory requirements and help increase scientific alignment."[13] During the first year of the Generic Drug Cluster, several agreements were reached including gathering and assessing data from participating agencies concerning an oncology treatment which may lead to a faster approval pathway for that type of drug and a need to establish a process for sharing data integrity concerns pertaining to bioequivalence and pharmacokinetic data in generic drug applications, among others.[14]

The International Council on Harmonisation (ICH) recognizes the opportunity for public health benefits by harmonizing technical and scientific standards for generic drugs across regulatory jurisdictions. In 2019, ICH released the Reflection Paper on Further Opportunities for Harmonization of Standards for Generic Drugs developed by the ICH Generic Drug Discussion Group and endorsed by the ICH Assembly. The paper recommends that proposed harmonization work should target scientific standards for generic drugs as well as the development of a series of ICH guidelines on standards for demonstrating bioequivalence for more complex dosage forms, recognizing that such harmonization "might reduce the need for comparative clinical endpoint studies and improve the sensitivity and reproducibility of bioequivalence determinations."[15]

Identifying priorities, areas of interest, and opportunities

With ongoing efforts to promote generic competition, notably by U.S. policymakers and regulators, identifying priorities, key opportunities for additional learnings, and particular areas of stakeholder interest can aid in the establishment of tools, resources, or guidance necessary to streamline processes and bolster the development of complex generic drug products for the market.

To this end, CRCG deployed a public survey asking what types of complex products, which methods of analysis to support bioequivalence, and which educational topics CRCG should prioritize. The top three product category selections were 1) injectables, formulations, and nanomaterials; 2) drug-device combination products; and 3) inhalation and nasal products. For educational topics, complex injectable and data analytics, including quantitative methods and modeling and simulation were among the top responses. An overwhelming 95.5% of respondents also agreed or strongly agreed harmonized international approach for regulatory standards for the development and approval of complex generic products should be a priority.[16]

USP recently hosted a virtual open forum entitled Technical and Regulatory Challenges for the Development of Complex Injectable Products, which focused on understanding development challenges and gaps in the compendia for these products. Based on the participant feedback, there are several areas where USP can focus and develop documentary standards such as *in vitro* dissolution methods, physicochemical characterization methods, complex excipient monographs, and physical materials such as molecular weight standards for the complex polymer analysis. These tools will help the complex generic manufacturers to expedite their product development.

Quality standards support development and approval of complex generics

Public standards, including monographs and General Chapters, help to ensure the quality of medicines by giving industry and regulatory authorities consistent analytical procedures and acceptance criteria to confirm product quality. They support the development, manufacture, distribution, and administration of safe and effective medicines, and can help to ensure a consistent level of

quality for complex and non-complex generic products. Numerous General Chapters, drug substance and drug product monographs, and reference standards are available within product classes identified as complex. Identification of standards currently available or the need for additional standards development to support complex generics throughout the product development lifecycle can assist manufacturers in producing quality products and ultimately increase the number of these products available on the market in timely manner.

Advancing the development of complex generic drug development and creating additional regulatory predictability for complex generics are vital to ensuring patients have access to a broad range of safe, quality medicines and to improve public health. The development of new methods and standards applicable to complex generics and that could be cross-cutting to other product categories can help foster the entry of safe and effective generic drug products to the market. USP takes an iterative approach to standards development, continuously evolving its standards from inception to official status to further revision in response to stakeholder input and advances in technology and regulatory science. Assessing standards related to APIs, excipients, and impurities as they relate to complex generics, as well as examining solutions such as tools to correlate *in vitro* and *in vivo* performance, emerging technologies, or digital standards (among others) may help to further develop the resources needed to encourage complex generic drug entry.

Looking ahead

Accelerating the development and approval of complex generic products is imperative to increasing access of these needed medications for patients. Effective engagement of industry stakeholders, regulators, and the public health community including patient organizations and health care practitioners can help to identify pertinent challenges and drive alignment of strategies and solutions to support the development and approval of complex generic products. USP is committed to enabling ongoing dialogues with regulators, manufacturers, policymakers, and other stakeholders to discuss the technical, scientific, and regulatory challenges involved in developing and marketing complex generic products, and has a team of USP staff experts working to support internal and external efforts related to current and emerging complex generic product issues.

References

[1]Food and Drug Administration. Generic Drugs: Questions & Answers. Accessed at https://www.fda.gov/drugs/frequently-asked-questions-popular-topics/generic-drugs-questions-answers.

[2]Katherine Tyner, PhD. An Overview of Complex Drug Substances and Complex Formulations – A Quality Perspective. Presentation to the Product Quality Research Institute. Accessed at https://pqri.org/wp-content/uploads/2019/04/2-Tyner_PQRI.pdf.

[3]Center for Drug Evaluation and Research. Manual of Policies and Procedures. Accessed at https://www.fda.gov/media/157675/download on May 12, 2023.

[4]Eglovich, Joanne. "FDA sees room for growth for complex generics." Regulatory Focus. 14 November 2022. Accessed at https://www.raps.org/news-and-articles/news-articles/2022/11/fda-sees-room-for-growth-for-complex-generics on May 12, 2023.

[5]Gottlieb, Scott. Reducing the Hurdles for Complex Generic Drug Development. Accessed at https://www.fda.gov/news-events/fda-voices/reducing-hurdles-complex-generic-drug-development on May 12, 2023.

[6]Association for Accessible Medicines (AAM). The U.S. Generic & Biosimilar Medicines Savings Report, September 2022. Accessed at https://accessiblemeds.org/sites/default/files/2022-09/AAM-2022-Generic-Biosimilar-Medicines-Savings-Report.pdf on May 11, 2023.

[7]Ibid.

[8]Brill, Alex. Potential Savings from Accelerating US Approval of Complex Generics, February 2021. Accessed at https://accessiblemeds.org/sites/default/files/2021-02/Potential-Savings-Complex-Generics-Feb2021.pdf on May 12, 2023.

[9]Eastern Research Group. Cost of Generic Drug Development and Approval. Feb. 2022. Accessed at https://aspe.hhs.gov/sites/default/files/documents/20e14b66420440b9e726c61d281cc5a5/cost-of-generic-drugs-erg.pdf on May 23, 2023.

[10]Controlled Correspondence Related to Generic Drug Development: Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. December 2022.over

[11]Food and Drug Administration. Pilot Program: EMA-FDA Parallel Scientific Advice for Hybrid/Complex Generic Products – General Principles. 15 September 2021. Accessed at https://www.fda.gov/media/152085/download on May 12, 2023.

[12]Thor S, Vetter T, Marcal A, Kweder S. EMA-FDA Parallel Scientific Advice: Optimizing Development of Medicines in the Global Age. Ther Innov Regul Sci. 2023 Mar 4:1–6. doi: 10.1007/s43441-023-00501-9. Epub ahead of print. PMID: 36871110; PMCID: PMC9985489.

[13]Food and Drug Administration. Generic Drug Cluster – One-Year Progress Report. Accessed at https://www.fda.gov/drugs/generic-drugs/generic-drug-cluster-one-year-progress-report on May 12, 2023.

[14]Ibid.

[15]International Council on Harmonisation. ICH Reflection Paper: Further Opportunities for Harmonization of Standards for Generic Drugs. Accessed at https://admin.ich.org/sites/default/files/2019-04/ICH_ReflectionPaper_GenericDrugs_Final_2019_0130.pdf on May 12, 2023.

[16]Stern S, Coghlan J, Krishnan V, Raney SG, Babiskin A, Jiang W, Lionberger R, Xu X, Schwendeman A, Polli JE. Research and Education Needs for Complex Generics. Pharm Res. 2021 Dec; 38(12):1991-2001. doi: 10.1007/s11095-021-03149-y. Epub 2021 Dec 24. PMID: 34950975; PMCID: PMC8732887.