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Expanding global access to complex generics: The case for regulatory convergence

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Complex generics (CGx) encompass categories of products that require specific studies beyond those needed for simple generic products to demonstrate therapeutic equivalence with innovator drugs. This article, adapted from presentations by the authors at the complex generics session at RAPS Convergence 2024, describes the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) regulatory approaches for complex generics/hybrid medicines and the results of studies by the United States Pharmacopeia (USP) in Brazil, China, India, Japan, and Mexico where approvals and regulatory and pharmacopeial requirements were assessed for selected complex products, both complex innovators and the corresponding complex generics, also marketed in the US. The benefit of convergence is discussed in the context of these findings and agency regulations.

Keywords – complex generics, convergence, hybrid medicines, pharmacopeial standards, product-specific guidelines

Introduction

Several publications address regulatory guidelines for complex products from the FDA and the EMA[1,2,3] as well as public forum discussions on international regulatory approaches.[4,5] In this context, regional and national regulations have been examined,[6-9] including by comparing requirements for products that fall under some of the complex generic categories characterized by the FDA.[3,10] A survey by the Center for Research on Complex Generics showed that over 95% of respondents, of whom more than 50% were from industry, agreed it is important to have a harmonized, international approach to regulatory standards for developing and approving CGx.[11] However, no agency, other than the FDA and EMA, has been identified as having explicit regulations for CGx as an overarching category of products.[3,10]

Background

For this article, the term *generic drugs* refers to copies of an *innovator product*, which is a new chemical entity developed by another company and not previously approved for use by a health agency. A generic drug needs to be therapeutically equivalent to the innovator product, which includes being a pharmaceutical equivalent in its composition, dosage form, and strength and being bioequivalent in the patient's exposure to ensure the same efficacy and safety profile as the innovator or reference product.

Among generics, for the FDA, *complex generics* are copies of complex products whose characteristics are described in more detail in the next section of this article and for which demonstration of therapeutic equivalence requires specific guidance and particular studies.

In the EU, the term *hybrid medicine* refers to medicines that depend in part on tests for reference medicines and in part on new data generated in clinical trials.

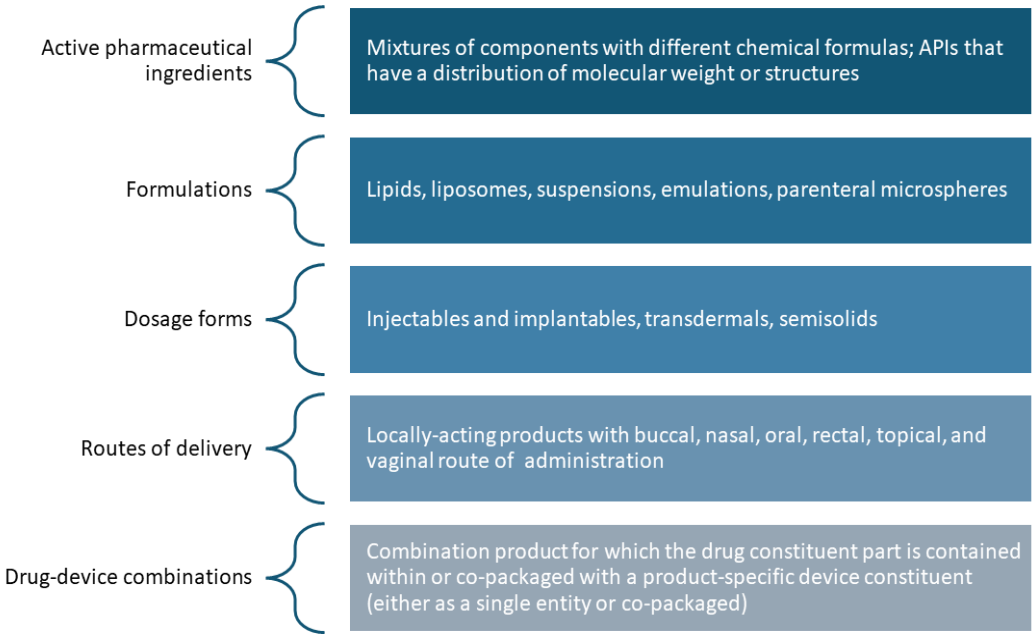
Generic medicines have had a significant positive impact on healthcare systems and patients by increasing access to medicines and lowering prices. This expanded availability of generics has led to other benefits, such as stable supply chains and the development of new treatment options. However, the generic industry also faces challenges related to increased market competition, market-entry legal challenges, and regulatory and other access barriers to international markets,[12] all of which can directly affect profitability.

Complex products offer many new alternatives to treating diseases and benefit patients as well as expanding opportunities for the generic industry to develop products that maintain profitable margins.[12] This includes both newly developed complex generics and others for which exclusivity and patent protections have recently expired or are about to expire. In this expanded and diversified market, regulatory agencies can enact programs and processes that foster the development, assessment, and approval of CGx while ensuring their safety and efficacy.

Classification of complex products

The FDA classifies complex products in categories of complexity based on defined structural and composition characteristics: complex active pharmaceutical ingredient (API), formulation, dosage form, route of delivery, and drug-device combinations (**Figure 1,** p. 3). An additional category "includes any product where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement."[13] The EMA classifies many products that fall under the FDA's CGx categories as hybrid medicines, for which there are also specific regulatory requirements.[14,15] However, as shown from analysis of examples taken from the literature, many follow-on versions of nonbiological complex drug products are registered in the EU under Article 10(1) for generics applications.[3]

Figure 1. The US Food and Drug Administration's characteristics of complex products



Adapted from MAPP 5240.10[13]

The EMA and FDA recognize that the information and studies recommended for proving therapeutic equivalence with the reference listed drug products may differ from those recommended for immediate- release oral solid dosage forms. Consequently, both agencies periodically develop and publish product-specific guidances (PSGs) that provides detailed information on the agencies' current thinking.

Moving toward regulatory convergence

FDA perspectives and initiatives[12]

FDA strategies relating to the development of generic products include harmonization of standards, streamlining of the approval process, mutual recognition and collaboration among agencies, quality assurance, and proper communications collaboration with industry.[12] These strategies, particularly the harmonization of standards and mutual recognition and collaboration demonstrate the interagency cooperation needed to reach convergence for CGx, the first in a series of steps that could result in benefits shown in **Figure 2** (p. 4).[12]

In addition to benefiting patients, the expanded access to novel CGx therapies creates opportunities for advancing and strengthening the overall generics industry in a cyclical process of interconnected factors (**Figure 3**, p. 4).[12]

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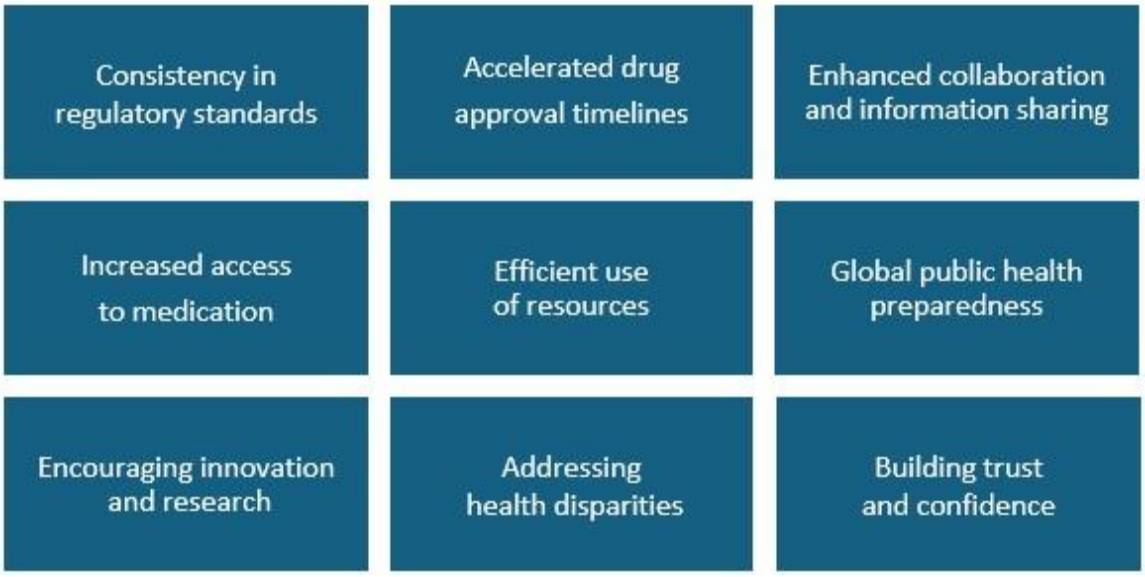
Figure 2. Benefits of harmonization[12,a]



[a]The table shows only categories with specific physical or compositional attributes; the examples provided are not comprehensive.

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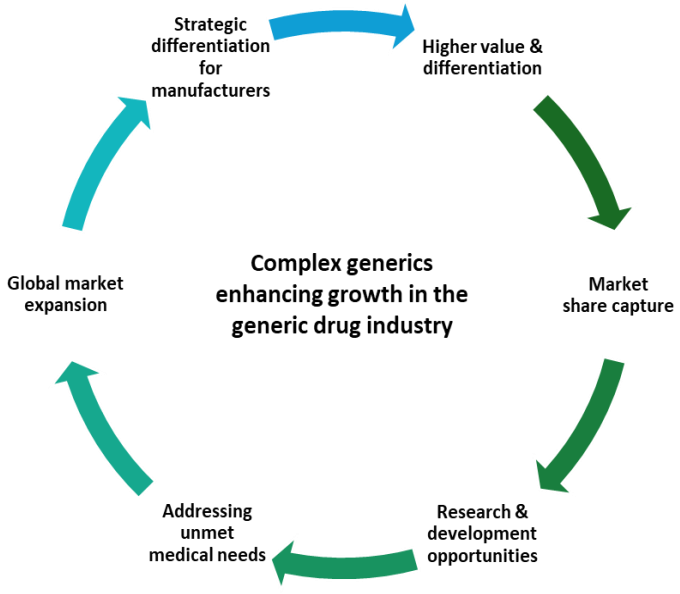
Figure 3. Complex generics revitalize the generic pharmaceutical Industry and market access



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A preliminary FDA analysis of CGx approved by the EMA during 2018-2023 showed that, from the perspective of FDA complexity status, the majority went through EMA's hybrid medicine pathway.[12]

EMA perspectives and initiatives[16]

The EMA does not have an explicit regulatory definition of CGx. However, most generics of what the FDA defines as complex products[13] will follow the EMA's regulatory pathway defined for hybrid medicines.[14] The correlation between both categories is established in the general principles of the FDA-EMA Parallel Scientific Advice (PSA) pilot program for complex generic/hybrid products.[15] However, some products processed under the EMA's generic pathway that would be considered CGx under FDA's regulations can be processed by the EMA as generics provided the product contains the same active substance as the reference medicine and is used at the same dose to treat the same disease.[12,14,16] Depending on various criteria, market authorization for hybrid medicines could be submitted through centralized or decentralized (based on mutual recognition that includes different countries simultaneously and individual national) procedures.[14,16]

The FDA and EMA participate in interagency initiatives, including the PSA pilot program, the Generic Drug Cluster (GDC), and the International Pharmaceutical Regulators Programme. These interagency initiatives serve as forums for discussing and advancing convergence for CGx.

Current interagency initiatives

FDA-EMA Parallel Scientific Advice Pilot Program

In 2021, the FDA and EMA established the PSA pilot program for complex generic and hybrid products so that the agencies could "concurrently consider and jointly exchange with applicants the agencies' views on scientific questions during the development phase of hybrid/complex generic products."[15] Initial participation by manufacturers has been limited,[17] but the eventual expansion of the program could facilitate the development of and accelerate approval for products in more than one jurisdiction. The results of industry discussions about development requirements with both agencies simultaneously will not necessarily lead to a harmonized approach. It is also important to note that the differences between the agencies regarding bioequivalence (BE) requirements for CGx will not be affected by the International Council for Harmonisation (ICH)'s recent guideline on bioequivalence for immediate release solid oral dosage forms (ICH M13A) because it does not address harmonization for CGx.[18] There are recommendations for future development of ICH bioequivalence guidelines for complex dosage forms and products.[19]

Generic Drug Cluster

The FDA established the GDC in 2021.[20,21] Several agencies other than the FDA and EMA participate in this international forum for the exchange of information and ideas, including Australia's Therapeutic Goods Authority, Health Canada,

Israel's Ministry of Health, the UK's Medicines and Healthcare products Regulatory Agency, and Swissmedic. The GDC allows agencies to discuss multiple regulatory issues for generic products and addresses CGx and some specific product types.[20,21]

International Pharmaceutical Regulators Programme

The IPRP does not specifically address overarching regulatory aspects of CGx, but it has a nanomedicines working group where agencies exchange varied information on types of products containing nanomaterials. With the participation of 16 agencies spanning the main regions of the world, the IPRP might be able to consolidate participants' shared approaches to reach consensus on standards and methodologies for products that constitute a significant part of complex generics in various categories.[22]

International regulatory landscape for selected US-approved products

To better understand the international regulatory requirements and availability of complex products beyond those approved by the FDA and EMA, USP conducted a study in 2022 in several countries across Africa, Asia, Europe, and North and South America. The findings showed that all the participating countries had registered and marketed complex products and CGx belonging to the FDA-characterized categories despite the lack of specific regulatory guidelines or explicit recognition of complex products by their respective agencies.[23,24]

At the 2024 RAPS Convergence, USP investigators shared new findings showing how regulations in Brazil, China, India, Japan, Mexico, and Turkey might affect CGx development and availability.[25] The study focused on complex products approved in the US and for which the FDA had developed PSGs. It aimed to identify two to four complex products in each FDA-defined category per country and at least four CGx per product, if available. The targeted data included manufacturer information, registration dates, and detailed country-level bioequivalence requirements and pharmacopeial standards. Comparable data were collected for FDA-approved products in the US.

Findings

Product identification. A systematic analysis in these countries identified 38 complex products across FDA complex product categories with an even distribution across categories (**Table 1,** pp. 7-8). Depending on their characteristics,[13] some products can be classified under multiple categories in other countries, as shown in the color orange in Table 1.

Of these 38 complex products, 78 products were identified across multiple markets (**Table 2,** p. 9). When the innovator of the product could be identified, it was the same innovator as the US product for at least 30% of products in each category. In the case of complex APIs, 73% were the same innovators as those in the US and the other markets.

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Table 1. Complex products identified in other countries[a]

Drug product	Country
Complex active pharmaceutical ingredient	
Enoxaparin injection	Brazil, China, Mexico
Ferumoxytol injection	India
Glatiramer acetate injection	Brazil, India, Mexico, Turkey
Glucagon injection	Japan
Liraglutide injection	Turkey
Omega 3 acid ethyl esters capsule	Mexico
Patisiran sodium injectable	Brazil
Semaglutide injectable	Brazil
Sevelamer carbonate tablet	China, India, Mexico, Turkey
Soybean oil injection	Japan
Complex dosage form	
Adapalene; Benzoyl peroxide gel	India
Butenafine hydrochloride cream	Japan
Cyclosporine ophthalmic emulsion	Brazil, China, India, Mexico
Difluprednate ophthalmic emulsion	India, Mexico
Doxorubicin HCl liposomes injection	Brazil, India
Fluocinonide topical ointment	Japan
Metronidazole topical gel	Turkey
Mometasone Furoate cream	China, India, Turkey
Mometasone Furoate topical ointment	Brazil, Mexico
Complex formulation	
Amphotericin B injectable	Brazil, China, Mexico, Turkey
Cyclosporine ophthalmic emulsion	Brazil, China, India, Mexico
Difluprednate ophthalmic emulsion	India, Mexico
Doxorubicin HCl liposomes injection	Brazil, India
Irinotecan Hydrochloride injectable	Turkey
Paliperidone Palmitate	China
Propofol emulsified injection	Japan
Timolol Maleate ophthalmic solution (gel-forming)	Brazil, Japan

[a]Orange text denotes drug products that fall into multiple categories in other countries.

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Table 1 (continued). Complex products identified in other countries[a]

Drug product	country
Complex route of delivery	
Acyclovir topical cream	Brazil, China, Mexico, Turkey
Brinzolamide ophthalmic suspension	Japan, Turkey
Diclofenac sodium gel	China, Japan
Lidocaine patch	India
Lidocaine topical ointment	Brazil, Mexico
Mometasone Furoate hydrate nasal spray	Japan, Turkey
Sumatriptan nasal spray	India
Complex drug-device combination	
Albuterol Sulfate metered-dose inhaler	Brazil, Mexico
Buprenorphine transdermal patch	Brazil, China, Mexico
Epinephrine auto-injector	Turkey
Ethinyl Estradiol; Etonogestrel vaginal ring	Brazil, India
Fluticasone Propionate nasal spray	China, India, Japan, Mexico
Fulvestrant prefilled syringe	Brazil, China, India, Mexico
Mometasone Furoate nasal spray	Japan, Turkey
Rivastagmine patch	Japan, Turkey

[a]Orange text denotes drug products that fall into multiple categories in other countries.

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Innovators' approval dates and lags between innovator and CGx approval. In the US, 75% of the complex generics surveyed were approved after PSG publication. Where registration dates were available for comparison, it was found that most US innovator registrations preceded innovator registration in other countries. Similarly, when dates were available for comparison, the time between PSG publication and first US generic approval was shorter than the innovator-to-generic approval time in other countries for 50% of complex route of delivery products and more than 60% of products in all other categories.

Generic availability. The numbers of CGx reported in this study for each category are indicated in Table 2. In each country, the types of products reported in the various categories are likely different because of the number of generics available. In addition, the total numbers of products and generics were expected to be higher in the US because the study design required identifying products registered in all countries that were also approved in the US. To allow for a better comparison of the availability of generics across countries, the total number of generics was averaged by the total number of products identified, as indicated in the last row of Table 2. Countries in the table are listed from the highest to the lowest number of generics averaged per product. India, the US, and Turkey had the highest averages.

Table 2. USP study: Number of complex generics in participating countries[a]

Category	India	US	Turkey	Japan	China	Brazil	Mexico	Total no. CGx per category
Complex API	12	21	7	2	8	6	11	**67**
Complex dosage form	15	29	4	4	6	6	6	**70**
Complex formulation	12	24	9	8	3	4	2	**62**
Complex route of delivery	6	24	5	11	8	7	5	**66**
Drug-device combination	17	26	18	8	4	12	5	**90**
Total number of CGx	62	124	43	33	29	35	29	**Total number of products in countries other than the US**
Total number of products per country	13	33	12	11	11	16	15	**78**
Number of CGx averaged per number of products	**4.77**	**3.76**	**3.58**	3.00	2.64	2.19	1.93	

API, active pharmaceutical ingredients; **CGx,** complex generics; USP, United States Pharmacopeia.

[a]The total number of generics was averaged by the total number of products identified, as indicated in the last row of the table. It shows countries listed from the highest to the lowest number of generics averaged per product, with India, the US, and Turkey (in dark orange) having the highest averages.

Previous study findings presented in 2023[23] and at the 2024 RAPS Convergence,[24] showed that for products containing preselected APIs, India and Turkey also had the largest number of CGx.

Bioequivalence recommendations. When information was available to compare bioequivalence recommendations for specific products in countries' general guidelines and the FDA's PSGs, the general guidelines and the FDA's PSGs were found to recommend a similar number of studies in 58% of the cases. In 42% of the cases, the number of studies recommended was lower or no information was available. Very few PSGs were identified for certain products in China and Mexico.

Pharmacopeial standards. In most categories, the USP-National Formulary (USP-NF) had more drug substance and drug product monographs per registered product than any other national or regional pharmacopeia.

Key takeaways

The results demonstrate clear advantages of the FDA's program for CGx development:

- FDA PSGs offer more extensive information on regulatory recommendations than what is available for most products in most

categories assessed in the six countries, likely contributing to faster US CGx development times.

- FDA PSGs provide in vivo/in vitro recommendations tailored for products, offering a better understanding of the agency expectations. At the same time, studied countries frequently lack detailed guidance that applies to the identified products. Therefore, many countries offer limited or no direction on quality attributes and bioequivalence for multiple products in the various CGx categories.

- The availability of USP-NF pharmacopeial standards across all categories for the drug substances and finished products helps facilitate faster development, regulatory compliance, and quality product development in the US and other countries where these standards are used.

The lack of detailed guidance on efficacy and safety assessments and quality attributes presents significant challenges for CGx development in other markets, potentially affecting development timelines and product quality.

Benefits of regulatory convergence for CGx

The study's findings underscore several advantages of the FDA's approach and the potential benefits of scientific harmonization among countries with CGx recommendations. First, countries must acknowledge these products' unique challenges in developing targeted guidelines and manufacturer guidance. Second, scientific alignment would accelerate the development timelines and approval of CGx, a benefit that would be further enhanced for products with common innovators across countries. Lastly, convergence on bioequivalence recommendations and recognition of pharmacopeial standards would streamline development and regulatory approval globally, enhancing patient access to these therapies.

Exploring convergence in regulatory settings

To address these challenges and capitalize on opportunities, regulatory agencies worldwide should explore existing programs implemented by regulatory agencies for convergence on CGx, such as the FDA-EMA PSA program, the FDA's GDC initiative, the IPRP, and the International Coalition of Medicines Regulatory Authorities, an informal forum of medicines regulatory agencies whose mission is to foster public health facilitating strategic leadership as well as enhancing cooperation.

Pharmacopeial collaboration to develop or adopt additional pharmacopeial standards is encouraged. USP-NF has over 250 official monographs, including general chapters, related to CGx and is working on the development of additional monographs.[26] As countries move toward convergence on CGx, and because regulations also encompass quality requirements, discussion for these types of products may be important for the Pharmacopeial Discussion Group,[27] which aims to harmonize pharmacopeial standards, particularly general

chapters. Current members include the European Pharmacopeia, the Indian Pharmacopeia Commission, the Japanese Pharmacopeia, and USP.

Conclusion

As CGx offer a path to additional supply options and increased competition, a concerted effort to converge and streamline regulatory processes across borders could help fully realize their potential. International cooperation and adoption of successful regulatory models will facilitate timely access to safe and effective CGx worldwide. Investing in regulatory convergence now is crucial for expanding global access to these vital therapies.

Abbreviations

CGx, complex generics; **EMA,** European Medicines Agency; **FDA,** US Food and Drug Administration; **GDC,** Generic Drug Cluster; **ICH,** International Council for Harmonisation; **IPRP,** International Pharmaceutical Regulators Programme; **PSA,** parallel scientific advice; **PSG,** product specific guidance; **USP,** United States Pharmacopeia; **USP-NF,** United States Pharmacopeia-National Formulary.

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