Global Regulatory Landscape of Complex Generics

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Objectives

1. Evaluate in ten countries the regulatory landscape and availability of complex products that fall under U.S. FDA defined categories

2. Examine approved complex products and inclusion of pharmacopeial quality standards for 12 active pharmaceutical ingredients across seven countries

Introduction

Regulatory agencies around the world establish guidelines and requirements for generic manufacturers to follow in the development, testing, and labeling of their products to ensure they meet the same standards as the innovator. These guidelines facilitate demonstration of therapeutic equivalence (TE) while reducing the need for extensive clinical trials. For most generics of small molecule immediate release oral solid and aqueous injection dosage forms, demonstration of TE usually follows standardized procedures.

The need for more effective treatments, including topical and parenteral dosage forms alongside improved patient compliance, have led to the development of non-biological complex products (NBCPs).* The U.S. Food and Drug Administration (FDA) broadly classifies these products in five main categories of complexity:[1] active pharmaceutical ingredients (APIs), formulations, dosage forms, routes of delivery, and drug-device combinations. Development and approval of generic versions of these types of complex products (Complex Generics/CGx) require studies beyond those described in the general guidelines for simple generics. To address the additional studies required for approval, and guide manufacturers through the challenges in development, the U.S. FDA publishes Product Specific Guidances (PSGs). Similarly, the European Medicines Agency (EMA) also recognizes that additional *in vivo* studies - beyond reliance on innovator studies - are required for the development and approval of generic versions of certain products, which are classified as hybrid medicines.[2]

Beyond the U.S. FDA and EMA, at agencies' websites from several countries in different regions, no specific classification and/or approval guidance are available for generics of NBCPs. To expand and better understand the international regulatory landscape of CGx, a more in-depth study was performed in ten countries from Africa, Asia, Europe, and Latin America, and the findings are presented here.

**The term NBCP is used since non-biological complex drugs (NBCDs) have been used for both complex APIs and the various types of complex finished products referred to by the U.S. FDA.[1, 3-4]*

Methods

Information was gathered during 2022 through primary research at regulatory agency websites, other publicly available regulatory and pharmaceutical market databases, national and regional pharmacopeias, and personal interviews with relevant stakeholders.

Results

In this work, the term CGx is utilized as a broad designation for products that pose challenges in demonstrating TE to complex innovator products, contrasting the well-established approach for small, low molecular weight medicines primarily in oral form. NBCPs serves as a more encompassing term including both innovators and subsequent generic versions.[3,4]

A. Preliminary Global Landscape of Regulatory Guidelines for Complex Generics

A search for guidelines referring to Complex Generics, Complex Products, or Hybrid Medicines was conducted on the Medicines Regulatory Authority (MRA) websites of the countries listed below with the terms Complex Generics, Complex Products, and Hybrid Medicines.

Africa: South Africa
Americas: Argentina; Brazil; Canada; Colombia; Mexico; Peru; USA
Asia/Pacific: Australia; China; India; Japan; Korea; Singapore
Europe: European Medicines Agency (EMA); UK; Russia; Spain; Switzerland
Specific guidelines on these categories were found on the websites of the U.S. FDA and the EMA, while Health Canada and the Therapeutic Goods Administration of Australia mentioned complex products in various contexts without specific guidelines for development or approval.

B. In-Depth Global Landscape of Regulatory Guidelines for Complex Generics

1. CGx products, quality information and relevant guidelines

Africa: Egypt
Americas: Argentina; Brazil; Mexico
Asia/Pacific: China; India; Japan; Korea
Europe: Germany; Turkey

Table 1. Availability of complex medical products and related quality & bioequivalence guidelines

Country	Complex API			Complex Formulation			Complex Dosage Form			Complex Route of Delivery			Complex Drug-Device Combination		
	In Country	Q	BE	In Country	Q	BE	In Country	Q	BE	In Country	Q	BE	In Country	Q	BE
Argentina	Y	Y	Y	Y	Y	Y	Y	NI	NI	Y	Y	Y	Y	NI	Y
Brazil	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NI	Y	Y	NI
China	Y	Y	Y	Y	Y	Y	Y	NI	NI	Y	Y	Y	Y	Y	NI
Egypt	NI	NI	NI	Y	NI	Y	Y	Y	Y	NI	Y	Y	Y	Y	NI
Germany	Y	NI	NI	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
India	Y	Y	NI	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NI	Y
Japan	Y	Y	NI	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Mexico	Y	NI	Y	Y	NI	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
South Korea	Y	Y	NI	Y	Y	Y	Y	Y	Y	Y	Y	NI	Y	NI	NI
Turkey	NI	NI	NI	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

In Country: Availability of certain products within the category **Q:** Quality information for certain products within category
BE: General bioequivalence guidelines/guidance for certain type of products within category **Y:** Yes **NI:** Information not identified

Key findings:
- Most countries have NBCPs in all categories
- Most countries have quality information on specific NBCPs as well as general BE guidelines for certain type of products within the different categories
- Complex APIs is the category with least information on quality and BE

2. Information on marketed products containing selected APIs

These assessments were performed in a subset of seven countries selected from those included in the previous section.

Americas: Brazil; Mexico
Asia/Pacific: China; India; Japan; Korea
Europe: Turkey

The APIs were selected based on a variety of criteria, including market size, prevalence of products in the region, and/or availability/absence of quality standards. **Table 2** shows the total number and availability of API-containing non-complex and complex products in the seven countries assessed.

Table 2. Therapeutic indication and availability of API-containing products across seven assessed countries

API	Therapeutic Indication	Number of countries with API-containing products		Number of API-containing products in all countries	
		Non-CGx	CGx	Non-CGx	CGx
Ambroxol	Expectorant	5	1	184	1
Amorolfine	Antifungal	2	5	7	5
Benzoyl Peroxide	Acne Treatment	1	7	2	39
Bromfenac	Ophthalmic Anti-Inflammatory	3	0	7	0
Domperidone	Antiemetic	5	0	86	0
Doxofylline	Asthma and Other Obstructive Lung Disorders	2	0	21	0
Fluticasone Furoate	Non-Allergic and Allergic Rhinitis	0	7	0	40
Gliclazide	Type 2 Diabetes Mellitus	6	0	110	0
Loxoprofen	Nonsteroidal Anti-Inflammatory	5	4	8	4
Metamizole Sodium	Pain Killer, Anti-Inflammatory	2	2	95	3
Nimesulide	Pain Killer, Nonsteroidal Anti-Inflammatory	3	4	72	50
Teneligliptin	Type 2 Diabetes Mellitus	4	0	28	0
Total Number of Products				620	142

Key findings:
- Most Benzoyl Peroxide and Fluticasone Furoate products were CGx and identified in all countries; for all other APIs and overall, the majority of identified products were non-complex
- No complex products were identified for five of the twelve APIs assessed

The total number of products containing the APIs - non-complex and complex - identified in countries is summarized in **Table 3.**

Table 3. Number of in-country products containing the selected APIs

Country	Non-CGx	CGx
Brazil	72	12
China	9	9
India	215*	20*
Japan	5	10
Mexico	80	10
South Korea	28	7
Turkey	211*	74*
TOTAL	620	142

***India and Turkey have the largest number of products, both of non-CGx and CGX, containing the selected APIs; in some cases, these include the same product in different presentations.**

Table 4 shows the different categories and number of CGx identified for the different APIs in every country assessed, while **Table 5** summarizes the availability of pharmacopeial standards for APIs and products in countries national or regional pharmacopeia (European Pharmacopeia for Turkey). For comparison, for these APIs, the availability of complex products in the U.S. FDA Orange Book and monographs in *USP-NF* is included.

Table 4. CGx categories per API identified in seven assessed countries

API*	Country**							
	Brazil	China	India	Japan	Mexico	South Korea	Turkey	USA - Orange Book
Ambroxol		RD-1						
Amorolfine	F/DF-1	RD-1	F/DF-1		RD-1		F/DF/RD-1	
Benzoyl Peroxide	F/DF-1	RD-2	F/DF-8	F/DF/RD-3	DF-5	F/DF/RD-2	F/DF/RD-18	F/RD-29 Topical Cream or Gel
Fluticasone Furoate	DDC-3	DDC-4	DDC-6	DDC-7	DDC-1	DDC-4	DDC-15	DDC-8 (1 OTC Nasal Spray)
Loxoprofen	RD-1	RD-1				F/DF-1	F/DF/RD-1	
Metamizole Sodium**					RD-2		RD-1	
Nimesulide	F/DF-6		F/DF-2 RD-3		RD-1		F/DF/RD-38	

Formulation and Dosage Form: F/DF; Route of Delivery: RD; Drug-Device Combinations: DDC
The characteristics of F, DF and RD are not mutually exclusive and sometimes the study classifies them together. F and DF are described together as a category in the U.S. FDA's MAPP 5240.10 (see reference 1).
*** The table does not include the five APIs for which no CGx were identified in the countries (see Table 2).**
**** Numbers after the various categories indicate the number of different products identified in the country and these includes in some cases the same product in different presentations.**

Key findings
- Complex Formulation(F) and/or Dosage Form (DF) were identified in all countries except China
- Complex Route of Delivery (RD) products was identified in all countries except South Korea and Turkey
- Benzoyl Peroxide CGx and Complex Drug Device Combinations (DDC) for Fluticasone Furoate were identified in all countries

Table 5. Drug substance and drug product monographs in countries' pharmacopeias

API	Country							
	Brazil	China	India	Japan	Mexico	South Korea	Turkey (Eur. P)	*USP-NF*
Ambroxol	No	API	API	No	Solution Tablets	No	API	No
Amorolfine	No	No	API	No	No	No	API	No
Benzoyl Peroxide	No	API Gel	API Cream Gel	No	Gel Lotion	No	API	API Lotion Gel
Bromfenac	No	No	No	API	No	No	No	No
Domperidone	No	API Tablets	API Suspension Tablets	No	Tablets	API	API	No
Doxofylline	No	API Injection Capsules	API Tablets	No	No	No	No	No
Fluticasone Furoate	No	No	No	No	No	No	API	No
Gliclazide	API	API Tablets	API Tablets	No	No	API	API	No
Loxoprofen	No	No	No	No	No	API	No	No
Metamizole Sodium	No	No	API	No	Tablets	No	API	No
Nimesulide	API	API Tablets	No	No	No	No	API	No
Teneligliptin	No	No	API Tablets ER Tablets	No	No	No	No	No

Key findings:
- Four of the seven countries lack compendial standards for most of the selected APIs
- Most pharmacopeias have no monographs for Drug Products (DPs) containing the selected APIs
- The *USP-NF* has drug substance (DS) and DP monographs only for Benzoyl Peroxide
- China, India and Turkey have the most monographs for these APIs

Discussion

The U.S. FDA and EMA recognize that, due to the complexity of certain products, the development of generics require specific guidance to ensure TE with the reference listed drug. For that purpose, they introduced the categories of Complex Generics (U.S. FDA) and Hybrid Medicines (EMA), through which they provide specific paths for registration and guidance to manufacturers to facilitate the development of generic versions of these complex products. None of the ten countries assessed in this research had a definition for these types of products nor specific guidelines to address their complexity; however, multiple products belonging to the categories of complex products as defined by U.S. FDA were identified, as well as general guidelines under which some products in these categories may have been registered.

In these countries, non-complex and complex products containing selected APIs were identified, but most national pharmacopeias have no standards for the DS and/or the DP. For the selected APIs, India and Turkey have the largest number of both products registered and pharmacopeial standards. This correlation raises the question of whether the availability of quality standards in these countries has facilitated the development and registration of related products.

The lack of specific regulatory information for assessing these types of products, as well as the lack of standards to assess their quality, uncovers the potential risks in their quality, safety, and efficacy. Following the type of collaboration established between the U.S. FDA and EMA, and as more complex generics enter the market in the U.S. and Europe, it is warranted to advocate for convergence in other countries, to facilitate their registration and ensure the access to patients of quality-assured, efficacious, and safe generic medicines.

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