Importance of Single Global Development of Generic and Biosimilar Medicines for Patient Access

Collaboration between University of Maryland and University of Michigan

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Final Report

October 2025

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Executive Summary

Background and Purpose

Generic and biosimilar medicines are fundamental to the sustainability of global healthcare systems. They account for 50-99% of all medicines dispensed in major markets and generated an estimated $445 billion in savings in the United States (US) alone in 2023. In Europe, generics account for 70% of prescriptions but only 19% of costs, while in Canada, they represent 76% of prescriptions and 22% of spending. This highlights a global shift towards more affordable medicines. However, despite the critical importance of generic and biosimilar medicines, regulatory fragmentation across major jurisdictions introduces inefficiencies that impede their development, market entry and patient access worldwide. This report presents real-world case studies illustrating how regulatory inconsistencies directly impact patient access to affordable, quality-assured medicines and offers targeted recommendations to advance global regulatory harmonization and international convergence.

Objectives

This report aims to:

1. Identify and analyze regulatory inconsistencies across major global markets (US, EU, Canada, and Japan) that impede global development of generic and biosimilar medicines.

2. Provide empirical evidence through case studies illustrating how regulatory fragmentation directly impacts patient access to affordable medicines.

3. Examine specific challenges impacting product development in the following categories: simple generics, complex generics, biosimilars, and orphan drugs.

4. Propose targeted recommendations for regulatory alignment that would enhance global patient access while maintaining robust safety and efficacy standards.

5. Support the advancement of a single global development paradigm for generic and biosimilar medicines to enhance healthcare affordability and accessibility to essential medicines worldwide.

Methodology

Our analysis integrates primary research data from over 50 stakeholder interactions (interviews, reports, questionnaires), which included companies and independent subject matter experts, with comprehensive secondary research data from regulatory databases, scientific literature, and industry reports. The study identified examples of products that are available to patients in one market but not others for which the primary reason is lack of single global development. Regions of primary focus were Europe (EU), Japan, Canada, and US.

Key Findings

The study identified 52 pharmaceutical products facing specific regulatory barriers that impede wide access to generic and biosimilar medicines across four categories: simple generics (18), complex generics (17), biosimilars (8), and orphan drugs (9). The top three regulatory barriers identified as significantly impeding global development include:

1. Duplicate Clinical Assessments: The most prevalent challenge faced by companies is the need to conduct redundant clinical studies with identical end points for different jurisdictions without scientific justification. Companies also noted differences in study design and population requirements across jurisdictions. For complex generics, these requirements can add $20-35 million in development costs and 12-24 months to timelines.

For biosimilars, costs can exceed $100 million for studies that yield no additional scientific insights. These cumulative costs and delays significantly influence market entry decisions.

2. Reference/Comparator Product Requirements: Region-specific requirements to use locally sourced reference/comparator products, even when demonstrably identical to those in other markets, create significant hurdles. Beyond regulatory requirements, access to reference/comparator products presents significant challenges particularly for REMS-protected products and orphan drugs. Pronounced price disparities and availability of reference/comparator products across markets further complicate the feasibility of development of generic and biosimilar medicines for certain markets.
3. Manufacturing and Production Challenges: Divergent regulatory specifications for purity, stability testing, packaging requirements, and facility inspections along with requirements for local manufacturing and variations in batch size and post-approval requirements compel companies to establish market-specific manufacturing processes and supply chains. These inconsistencies substantially increase development costs without measurable benefits to product quality or safety.

Many of these regulatory inconsistencies lack scientific justification, and their impact on financial and operational aspects of product development are significant and far-reaching.

Impact on Patient Access

These regulatory barriers disproportionately affect smaller markets and rare disease treatments. Notably, 24 of the 52 identified products (46%) appear on the WHO Essential Medicines List (EML), highlighting the critical importance of these medicines to global public health. Companies frequently abandon development of these products for certain markets when regulatory requirements become economically unfeasible, leaving patients in those regions without access to affordable treatment options.

Recommendations

1. Establish legislative and regulatory pathways to allow use of foreign comparator products to reduce development costs while maintaining scientific standards for establishing bioequivalence/equivalence.
2. Align technical standards across regulatory agencies for dissolution testing, impurity thresholds, and manufacturing specifications, eliminating discrepancies that lack scientific rationale.
3. Streamline development pathways for complex products and biosimilars by eliminating redundant clinical study requirements when sufficient analytical and other clinical testing evidence exists.
4. Enhance regulatory collaboration through work-sharing initiatives similar to the EU's centralized procedure and expand programs like the International Coalition of Medicines Regulatory Authorities (ICRMA) collaborative assessment and inspection pilot programmes, Access Consortium and FDA-EMA Parallel Scientific Advice Pilot Program to include other major countries.

Conclusion

The urgency for regulatory harmonization cannot be overstated. Every day that passes with fragmented requirements directly translates to patients being denied access to affordable, life-saving medicines. Complete harmonization is not easily achievable, however, targeted alignment in the critical areas identified in this report, while maintaining robust safety and efficacy standards, should be treated as a global health priority, as it would yield substantial benefits for patients worldwide.

Introduction

Generic and biosimilar medicines - impact on healthcare systems and economics

Generic and biosimilar medicines serve as cornerstones of sustainable healthcare systems globally, providing over 50-99% of all medicine volume in key markets worldwide (1,2). Generics are pharmaceutically equivalent, small-molecule versions of brand-name drugs demonstrating analytical sameness and bioequivalence (BE), whereas biosimilars are complex biological products that must establish similarity in quality, safety, and efficacy to approved biotherapeutics (3).

These medicines transform healthcare economics and patient access globally, including the largest pharmaceutical markets: the US, EU, Japan, and Canada (4,5). The US leads generic adoption, with generics constituting over 90% of prescriptions but merely 12% of expenses (4,6,7). In 2023, approved generics and biosimilars generated $445 billion in savings for the US healthcare system, contributing to $3 trillion in savings over the past decade (6). Similarly, in Europe, generics represent 70% of prescriptions yet 19% of costs, whereas in Canada, they comprise 76% of prescriptions while accounting for 22% of spending (5,8,9). Japan has seen generic penetration rise dramatically from 32.5% to 78.3% between 2005 and 2020 (4,10,11). US Food and Drug Administration (FDA) data demonstrated that competition drives affordability, with six or more competitors reducing generic prices by more than 95% compared to brand alternatives (12). Biosimilars, though at earlier adoption stages, are projected to generate over $290 billion in cumulative global savings through 2027 (5,9). Europe has led the world's largest biosimilar market since 2006, outpacing the US where adoption was initially slower (4,5,9). Recently, however, US biosimilar uptake has accelerated significantly due to policy changes and patent expirations. Notably, 40% of total US biosimilar savings since their 2015 introduction occurred in 2022 alone

(13). Beyond healthcare cost savings, these medicines expand patient access to critical treatments – biosimilar competition in immunology has increased its usage by 5% in Europe as more patients have access to treatments at lower costs (5). Across major developed markets, there has been a 163% increase in utilization rate per 100,000 patients for immunology therapies over the past decade. Like generics, competition between biosimilar manufacturers also leads to further reductions in treatment costs. For instance, in Europe it was shown that 5 or more biosimilar competitors for one product can reduce prices by 70%, while in the US, competition between oncology biosimilars has saved cancer patients more than $22 billion since market entry (1,13–16).

Regulatory approval process for generics and biosimilars by major global regulators and regulatory divergences

Market entry for generic and biosimilar medicines is governed by regulatory bodies independently across major markets. The FDA approves generic drugs through the Abbreviated New Drug Application (ANDA) pathway, requiring demonstration of pharmaceutical equivalence and BE to an FDA-designated previously approved reference listed drug (RLD; comparator product) that serves as the standard for all studies (17). However, when the RLD is unavailable, an alternative reference standard may be selected for BE studies. For complex generics i.e. products with complex active ingredients, formulations, routes of delivery, or drug-device combinations, the FDA often requires additional evidence beyond standard BE-pharmacokinetics (BE-PK) studies, including advanced analytical characterization and specialized testing (18,19). Furthermore, the FDA issues new and revised Product Specific Guidances (PSGs) for generic drug products on a quarterly and as needed basis to provide its current thinking and recommendations on the evidence and methodology needed to support approval of generic products, which in general is beneficial and required to bring safe and effective medicines to patients faster (20). Biosimilars in the US are approved under the 351(k) pathway created by the Biologics Price Competition and

Innovation Act (BPCIA) of 2009, employing a risk-based ‘totality of evidence’ approach that requires comprehensive analytical characterization, animal studies, and/or clinical evaluations to demonstrate biosimilarity with the reference/comparator product (21). While the reference standard (comparator product) must be FDA-licensed, a non-US licensed comparator may be used in certain studies if a scientific bridge to the US-licensed reference product is established. These follow-on biologics may seek an additional “interchangeability” designation, which until recently required switching studies but was revised in June 2024 when the FDA issued updated draft guidance no longer requiring such studies (22,23).

The European Medicines Agency (EMA) and the National Competent Authorities (NCAs) of the 27 European Union (EU) Member States and the European Economic Area (EEA) jointly conduct the scientific evaluation and safety monitoring of medicines in the EU. The EMA and NCAs evaluate generics for approval under Article 10(1) of directive 2001/83/EC, with similar BE requirements to the FDA but offering greater procedural diversity through centralized, decentralized and mutual recognition pathways (24,25). While the FDA uses the term “complex generics” to describe generic products with complex active ingredients, formulations, or delivery mechanisms, the EU does not have an official designation for this category. However, the EU classifies such products as ‘hybrid medicines’ under Article 10(3), which require additional pre-clinical and/or clinical studies when strict generic similarity criteria are not met (26,27). Notably, the EU regulatory framework does not explicitly permit the use of foreign reference/comparator products for either standard generics or hybrid medicines, requiring comparisons with EU-sourced reference/comparator products (25). For biosimilars, the EMA pioneered the first dedicated regulatory approval framework in 2004, continuously refining it through product class-specific guidelines that increasingly emphasize analytical characterization while minimizing animal studies (28,29). Unlike their approach to generics, the EMA does allow the use of foreign reference/comparator products for biosimilars to facilitate global development (30). The EMA

evaluates biosimilarity and considers all approved biosimilar medicines interchangeable by default (31–33).

Health Canada (HC) follows the Abbreviated New Drug Submission (ANDS) pathway for generics approval, requiring BE to a Canadian Reference Product (CRP), comparator product, with provisions for using foreign comparator products when demonstrated to be identical to the CRP (34–38). While Canada's basic BE standards align with FDA and EMA requirements, it has no distinct pathway for complex generics. For biosimilars, HC's regulatory approval pathway permits the use of non-Canadian reference/comparator products under specific conditions (39). Furthermore, Canada has no specific interchangeability evaluations and defers substitution decisions to provincial authorities (40).

Japan's Pharmaceutical and Medical Devices Agency (PMDA) categorizes generic products for approval by dosage form rather than complexity, with standard BE requirements (41,42). Japan's biosimilar approval framework, established in 2009, employs a stepwise approval approach that permits use of non-Japan sourced reference/comparator products if comparability is demonstrated, but requires approval for all indications where the reexamination period has expired (43,44). Japan's regulations lack a formal interchangeability designation, with the naming system preventing automatic substitution at the pharmacy level.

While regulatory authorities share common regulatory principles, inconsistent regulatory requirements, interpretation and application of regulatory guidances across jurisdictions creates significant barriers for development of generic and biosimilar medicines for global markets limiting global availability of these medicines and thereby patient access worldwide (45–51) . Generic and biosimilar medicines typically have lower profit margins compared to brand-name drugs owing to increased competition, reduced pricing at market entry compared to brand alternatives and research and development costs. While biosimilars may have higher margins compared to

generics, they are still lower than those of brand-name biologics. The fragmented global regulatory landscape particularly impacts biosimilars, with approximately half of biologics coming off patent in the next decade potentially having no biosimilar competitors due to prohibitive development costs (51). Biosimilar development costs up to $300 million and takes up to 9 years, largely attributable to comparative clinical trials required by multiple authorities. A review of 70 countries identified critical divergences in regulatory requirements across markets including local reference/comparator specification, animal studies, clinical design, and labeling formats to name a few (47). These discrepancies force companies to prioritize profitable markets while neglecting regions where access to critical medicines is already limited (45).

Complex generics face similar challenges due to market-specific development approaches and different reference/comparator standard requirements (1,52). A review of regulatory frameworks across the US, EU, and Canada reveals disparate classification and evaluation methods: the FDA applies standard ANDA pathways with supplemental guidance, the EU employs either generic or hybrid medicine pathways based on data requirements, and Canada lacks clear guidelines, evaluating applications case-by-case basis (52). A notable case study of enoxaparin illustrates how identical products undergo entirely different regulatory pathways across jurisdictions (52). Enoxaparin sodium, a low-molecular weight heparin with complex molecular diversity, is approved via the ANDA pathway with product-specific guidance in the US, whereas in the EU it follows a ‘biosimilar’ pathway with centralized procedure, and in Canada is regulated as a biologic product by HC’s Biologics and Genetic Therapies Directorate (BGTD) due to its diverse nature.

Evidence suggests that some of the regulatory requirements lack scientific justifications. Analysis of biosimilar approvals found that expensive confirmatory efficacy trials offer minimal discriminatory value, with European regulators noting that quality data and PK studies alone justified differences in quality attributes (48,50,51). Animal testing still persists in various jurisdictions, including Argentina, Brazil, Dominican Republic, China, Korea, Thailand, Iran, and

Iraq, despite evidence that most animal species lack receptors necessary for biological products' mechanism of action (49,53). For generics, differences in technical specifications, varying assay criteria and inconsistent testing protocol requirements by the regulatory bodies across the globe create unnecessary barriers forcing companies to develop different methodologies, use different raw materials and perform extra characterization studies to satisfy different regulatory requirements (45,46). Complex generics face greater challenges with demonstrating equivalence owing to their inherent complexity and this challenge is only amplified by the divergence and ambiguity in regulatory approaches and guidances, that are subject to revisions, across regulators (52).

Jurisdictions with highest biosimilar uptake, including EU and United Kingdom (UK), feature product-specific guidance and flexible regulatory approaches, while markets with additional barriers such as the US (with its 12-year exclusivity period) show lower adoption rates (54). Overall, the absence of harmonized approaches increases development costs and delays market entry, ultimately limiting patient access to affordable medicines across both biosimilars and generics categories (52,54).

Global harmonization of regulatory process and impact

To address these regulatory divergences, several international initiatives have emerged to streamline development and approval processes across jurisdictions (Table 1). The World Health Organization (WHO) developed the Prequalification of Medicines Programme (PQP) in 2001, to ensure quality of essential medicines while facilitating access to affordable generics in resource-limited settings (55). By establishing transparent evaluation standards for non-originator medicines, WHO PQP created a quality benchmark adopted by major funding organizations, enabling 6.5 million of 8 million global HIV patients to access prequalified antiretrovirals by 2012. WHO has further advanced international consensus on BE assessment for generics and

biosimilar evaluation, and selection of comparator products for assessment of generics (3,56,57), with the new 2022 guidelines indicating PK/pharmacodynamics (PK/PD) studies could replace clinical efficacy studies for biosimilars given sufficient evidence (58).

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) expanded from innovative products to include guidelines for generics and biosimilars (59,60). The founding regulatory members of ICH consists of EU/EMA, FDA, and PMDA, and includes other regulatory members such as HC and Swissmedic, among many others. Key harmonization standards include ICH M9 guideline on biowaivers, M10 on bioanalytical method validation, and more recently the finalized M13A guideline for BE assessment of immediate-release (IR) solid dosage forms (61–63). ICH M13B, focused on BE for additional strengths of IR solid oral dosage forms, was released as a draft guideline in February 2025 and is currently undergoing public consultation (64). Meanwhile, M13C is in development as the next planned guidelines in the series, which will address complex BE assessments for special cases such as highly variable drugs, drugs with narrow therapeutic index, and complex BE study design and data analysis considerations for IR solid oral dosage forms (65).

Complementing these efforts, the International Pharmaceutical Regulators Programme (IPRP), formed in 2018, composed of about 26 national and regional regulatory authorities including the FDA, EMA, HC, PMDA, MHRA, HAS (Singapore), and ANVISA (Brazil), among others. The IPRP facilitates regulatory convergence through information exchange rather than formal guidelines (66). Its working groups have identified significant regulatory divergences while exploring opportunities for convergence in areas such as biowaivers, foreign comparator acceptance, and requirements for waiving in vivo studies for various dosage forms (67–69). Similarly, the Access Consortium, established in 2020 with the regulatory authorities being Australia, Canada, Singapore, Switzerland, and the UK, implements a collaborative model where one agency leads evaluation while other members provide feedback, though benefits remain limited to member countries (70). By leveraging the Work-sharing Initiatives and joint application pathways Access

enables reduced duplication of effort by both the industry and regulators and facilitates simultaneous approval in up to 5 markets (71). The International Coalition of Medicines Regulatory Authorities (ICRMA) have implemented initiatives, including collaborative assessment and inspection pilots that have achieved simultaneous multi-region approvals for generics and biosimilars (72,73). This organization comprises of 24 members including the EU, US, Canada, Japan, UK, Australia, Brazil, China, and others, and 15 associated authorities.

More targeted initiatives include the FDA-EMA Parallel Scientific Advice Pilot Program, initiated in 2021, which enables applicants to engage with both agencies during complex generic development (27,74,75). Additionally, the Generic Drug Cluster led by the FDA alongside the EMA includes other authorities like MHRA (UK), HC, Swissmedic, Israel Ministry of Health, and TGA (Australia). They provide a confidential forum for resolving specific review issues without formal guideline development (76,77).

Despite these promising initiatives, substantial barriers to implementing single global development remain. This paper presents empirical evidence demonstrating how regulatory fragmentation across the FDA, EMA, HC, and PMDA directly impacts patient access to generic and biosimilar medicines. Through detailed case studies across therapeutic categories – simple generics, complex generics, biosimilars, and orphan drugs – we identify specific medicines available in one of these major markets but not others primarily due to divergent regulatory requirements. For examples within each category, we discuss recommendations for regulatory alignment that would enhance patient access while maintaining robust safety and efficacy standards.

Table 1: Summary of global regulatory harmonization efforts.

Organization	Harmonization of Guidelines	Biosimilars Guidelines	Generic Drug Guidelines	Work-sharing & Simultaneous Reviews	Manufacturing Standards (GMP)	Pharmaco-vigilance & Safety	Global Regulatory Collaboration
International Council for Harmonization (ICH)	✓	✓	✓		✓		✓
World Health Organization (WHO)	✓	✓			✓	✓	✓
Access Consortium		✓		✓			✓
FDA-EMA Bilateral Pilot Programs		✓	✓	✓		✓	✓
International Pharmaceutical Regulators Programme (IPRP)	✓	✓	✓		✓	✓	✓
International Coalition of Medicines Regulatory Authorities (ICMRA)					✓	✓	✓
Generic Drug Cluster (GDC)			✓	✓			✓

Methodology

Primary research – interviews

Outreach to generic and biosimilar drug companies was initiated in October 2024. Twenty-three companies were identified for interviewing by the project team in collaboration with the International Generic and Biosimilar Medicines Association (IGBA). The focus was to assess the potential benefit of single global development, including identifying example products which may (or would) have in the past benefited from harmonized global product development. Regions of primary interest were EU, Japan, Canada, and US. The project team conducted structured interviews with companies across key therapeutic categories: biosimilars, simple generics, complex generics, and orphan drugs. The goal of these interactions was to assess regulatory pain points and challenges faced by these companies in accessing global markets for generic and biosimilar medicines with major focus on US, EU, Canada and Japan. Relevant pain points and challenges faced by these companies in other jurisdictions within MENA (Middle East, and Africa), NAMER or NORAM (North America), APAC (Asia-Pacific), and LATAM (Latin America) were also

captured. Examples of products that are available to patients in one market but not others for which the primary reason is lack of single global development were collected during these interactions. Seventeen companies expressed their interest in providing their feedback with twelve companies engaged during the project period. Data was collected from >50 interactions with these companies and additional independent subject matter experts, which included several rounds of interviews, reports and questionnaires.

Secondary research – literature and databases

Information was obtained from peer reviewed articles published in scientific journals, reports published by industry organizations and associations such as World health Organization (WHO) Association for Accessible Medicines, Canadian Generic Pharmaceutical Association, Medicines for Europe, International Generic and Biosimilar Medicines Association, publicly available databases published by WHO, FDA, EMA, HC and PMDA. Dates for drug approval were obtained from databases published by FDA, EMA, HC and PMDA when available and open-source information such as press releases. Appropriate references have been provided for all information obtained from secondary research.

Table 2: Interview structure and examples of questions.

Objective of Discussion

A. Identify scope of generic/biosimilar products available in one country/region but not others
B. Identify reasons such products are available in one country/region but not others
C. Identify patient population impacted through lack of available generic/biosimilar medicine and extent of impact (patient lives lost, disease/condition progression)

Preliminary interview questions

1. What products do you manufacture that are available in one country/region but not others?
    - Companies may wish to consider products that are most challenging to develop and those with the greatest potential patient impact (either in terms of potential patient population or severity of disease/condition). (Consider the scope for this project: simple generics, complex generics, biosimilars, orphan drugs.)
2. What products are you considering developing for which single global development would help the business case?
3. Why did you choose not to pursue development in certain countries/regions? Please consider:
    - Scientific and regulatory hurdles (e.g., different approval standards, having to conduct more BE studies, etc.). These are the focus for this project.

- Supply chain limitations (e.g., limited or no manufacturing presence in certain countries/regions; limited or no distribution network). Out of scope for this project.
- Pricing (e.g., even if the product was approved, the way it is paid for would make it unprofitable or not profitable enough to justify the cost. In this case, please indicate if a streamlined regulatory process—in which costs are reduced—would help improve the business case).
- While pricing is out of scope, if one of the reasons is "business strategy" E.g., if your business focus is limited to certain geographies regardless of how easy it may be to introduce a product in a country/region, we would like to understand if the underlying reason for the business strategy is driven by lack of single global development (i.e., scientific and regulatory hurdles).
- IP issues are out of scope for this project.

4. For a drug marketed in one country/region, if you sought approval of that drug in another country/region but were denied approval, what reason was given? How did this experience compare to countries/regions where approval was granted? (i.e., was the same issue identified by authorities who did approve the drug but resolution was easier; was the issue not identified at all by authorities who did approve the drug)
5. What is the potential market for the drug in markets you chose not to pursue or were denied approval in? (The ideal metric here is number of patients). Consider that it may be possible from a financial figure to determine the number of patients impacted; e.g., if a potential market is $100 million, that figure may have been derived from an analysis of how many patients would use the product—that's our target.
6. For each drug available in one country/region but not another, what treatment alternatives exist for patients in countries/regions without the drug?
7. What is the monetary cost to patients for such alternatives?
8. What is the non-monetary cost to patients resulting from lack of access? (e.g., lives lost, disease/condition worsening)
9. What solutions do you believe health authorities can implement to improve patient access to generic/biosimilar medicines?

Additional interview questions

What agency (or agencies) required the following when you believe one was not scientifically needed? How long was the approval delayed, particularly if finally approved and timeframe from another agency who did not see an issue is available to assess impact on patients? If not yet approved, what has been the approval delay timeframe? If a product was abandoned due to this issue, knowing that is also helpful.

- a human factors study (and for which drug product)
- a "local" reference product that was expensive (and for which drug product)
- a "local" reference product that was not available (and for which drug product)
- a "local" clinical study [e.g., local BE study] (and for which drug product)
- a clinical endpoint study (and for which drug product)
- a "better" impurity profile (and for which drug product)
- unique packaging requirements (and for which drug product)
- unique immunogenicity requirements (and for which drug product)
- unique molecular weight requirements (and for which drug product)
- unique Mossbauer requirements (and for which drug product)
- unique forced degradation requirements (and for which drug product)
- unique DMF requirements (and for which drug product)
- unique dissolution requirements (and for which drug product)
- unique strength requirements (and for which drug product)
- a large clinical sample size requirement (and for which drug product)
- a large clinical sample size requirement (and for which drug product)
- unique stability testing requirements (and for which drug product)
- unique API production/manufacturing hurdles (and for which drug product)
- have differing interpretation of guidance, e.g.: ICH Q5E and ICH M9, i.e., use of surfactants (and for which product)

Results

Overview of general challenges faced during development of generics and biosimilars

Based on primary research conducted with generic and biosimilar companies, we identified several recurring challenges that hinder the development of generic and biosimilar medicines for a global market. These challenges represent significant barriers for efficient development and timely patient access for these medicines. A summary of the key challenges faced by companies when developing generic and biosimilar medicines across different jurisdictions is provided in Table 3.

Table 3. Types of Challenges. Tabulated are the major categories of regulatory challenges faced by companies during development of generics and biosimilars. Number 1-9 represent information from 9 companies we interacted with, and X represents the regulatory challenge mentioned by these companies during these interactions.

Challenges	Generic/Biosimilar Company								
	1	2	3	4	5	6	7	8	9
Clinical Assessment Requirements	X	X	X	X	X	X	X	X	X
Reference Product Requirements	X	X	X	X	X	X		X	X
ICH Guideline Implementation			X	X			X	X	X
API Requirements			X	X	X			X	X
Biowaiver Requirements	X	X		X				X	X
Immunogenicity Assessment Protocols			X	X	X	X		X	
Manufacturing and Production	X	X	X		X	X	X	X	X

Amongst multiple challenges that impacted global development of generics and biosimilars, the major themes that emerged include need for duplicative clinical assessments, varying and demanding reference/comparator product and API (active pharmaceutical ingredient) requirements, inconsistencies with ICH guideline implementation, biowaiver requirements, immunogenicity assessment protocols, manufacturing and production requirements. While clinical assessment requirements, reference/comparator product requirements, and manufacturing hurdles emerged as the most prevalent challenges (addressed in detail in subsequent sections), four additional barriers were consistently identified across interviews.

ICH guideline implementation

Companies noted that ICH guidelines are paving the way to mitigate challenges, especially with the introduction of key guidelines such as M9 and M13 series, which significantly reduce the need for in vivo BE studies. However, it was noted that the regulators take time to implement these guidelines and may have additional requirements, e.g.: based on ICH M9 companies could apply for Biopharmaceutics Classification System (BCS) based biowaiver if API is highly soluble, however under the Q&A Mexico does not accept this biowaiver and requires additional studies. Another example of differing adoption of guidance included ICH Q5E and ICH M9 in use of surfactants and alternate options for dissolution testing. Additionally, ICH guideline interpretation presents substantial challenges despite harmonization efforts. Companies reported varying implementation of ICH guidelines across jurisdictions, particularly for complex products (ICH Q3B (R2)). The ICH process in general was reported as long, with discussions on important topics taking several years. Several companies noted that some regulatory authorities only partially implement ICH guidelines, especially with regards to biowaivers (ICH M9 and M13). This selective implementation creates additional complexity, with alternate approaches being allowed in one jurisdiction and requirement for extensive characterizations studies to demonstrate BE in other jurisdictions.

API requirements

API purity requirements vary significantly across regions, necessitating market-specific formulations, raw materials quality and manufacturing processes. Japan was frequently cited as a market requiring additional purification steps beyond what other regulators demand without clear scientific rationale and some countries, such as Brazil, require additional API validation criteria, which requires manufacturing separate country specific batches. Companies mentioned that with peptides, they need to optimize manufacturing processes specifically to meet impurity levels for US approval despite having marketed the same product in Europe for years with differing impurity thresholds. These additional requirements significantly impact the cost of API without benefits to product quality or safety, and often outweigh the business case, for example, with simple oral products where margins are low and complex injectables/inhalers where there are additional costs related to device component, excipients and manufacturing. This has led companies to focus on larger markets such as US and EU for early market entry, and delaying entry in markets with additional requirements to allow time for additional batches, stability and other testing. It was also noted that some countries mandate local manufacturing of both reference/comparator product and the test drug for BE studies. This requirement adds complexity to production logistics, drives up costs for setting up local facilities or contracting local partners, limits scalability and delays drug development timelines. Most regulators require Drug Master Files (DMFs) to be registered in local jurisdictions, which add enormous time and cost to third-party API manufacturing with very little return on investment. This also automatically limits the options of third-party API manufacturers that could work with generic companies for those jurisdictions.

Biowaiver requirements

Biowaiver requirements differ substantially between authorities, complicating development of products with multiple proportional strengths. Many jurisdictions have begun implementing

aspects of ICH M9 guidelines which has been finalized and M13B which remains as a draft and has not yet been finalized. However, companies continue to face challenges due to contradictory dissolution testing methodologies and acceptance criteria across regions. Canada requires one unit per vessel during dissolution testing while the EU accepts multiple units, directly impacting test outcomes for low-solubility drugs. Surfactant use in dissolution media highlights further divergence: US allows surfactants in all three standard pH media with justification, Canada permits variable surfactant levels for different strengths to ensure “equivalent driving force”, while EU prohibits surfactants in the standard media altogether. These differences in requirements necessitate development and validation of country-specific dissolution methodologies and add to the overall product development cost and time needed for product approval.

Biowaiver requirements for proportional similarity across different strengths of same drug product differ across regions. Lookalike formulations across different strengths are acceptable in US but not in EU, where multiple BE studies need to be conducted as compared to US. These differences in biowaiver approaches create substantial financial burdens, costing up to $1 million in development costs and timeline delays extending three times longer than necessary. For immediate-release (IR) tablets with directly proportional formulations, a generic company described being required to demonstrate that dissolution conditions for each strength were discriminatory in Canada, while such requirements were not imposed in other jurisdictions, such as EU which readily issued biowaivers.

Immunogenicity requirements create additional challenges for complex injectables and biosimilars. The FDA typically requires comprehensive in vitro immunogenicity testing while European authorities take more pragmatic approaches, especially for peptides. One company described spending 12 years navigating evolving immunogenicity requirements for product approval, citing constantly changing expectations and challenges with increasingly sensitive methodologies, that focus more on analytical methods than meaningful clinical differences.

While progress towards harmonization is evident in certain areas, significant regulatory divergence continues to negatively impact global development of generic medicines. These challenges collectively impact companies' decisions about which markets to pursue, particularly affecting development for smaller markets and those treating rare diseases with significant implications for patient access to these medicines.

I. Clinical assessment requirements

Unnecessary clinical trial duplication without clear scientific rationale emerged as the most prevalent challenge faced by generic and biosimilar companies. Analysis of interviews from these companies revealed redundant clinical studies requirements by different regulatory authorities, despite these studies targeting identical endpoints. This redundancy was noted to be often cost prohibitive and significantly impacted development timelines, resource allocation, and ultimately, patient access to affordable medications.

Study design differences

A fundamental inconsistency exists in BE study designs across major markets. Multiple companies reported that different regulatory authorities demand different approaches for the same products. The US typically required both fasting and fed studies, while the EU often accepted fasting studies alone. This is further demonstrated by an oral oncology product, where the EU recommended a multi-dose cross-over study in patients with specific conditions, while the US recommended a single-dose cross-over study in healthy volunteers – creating a situation where completely different studies were required for the same product. These divergent requirements force companies to conduct additional studies that add little scientific value but significant costs. However, in a recent significant regulatory shift, the FDA revised more than 800 PSGs in October 2024 to align with ICH M13A guidelines, now recommending only one BE study (under either fasting or fed conditions) instead of requiring both for most IR solid dosage forms (78). While this represents important progress toward reducing redundant testing, it is important

to note that the guidelines have not yet been implemented by all ICH members, which may delay the full realization of harmonization benefits.

For narrow therapeutic index drugs, the difference becomes even more pronounced. Some companies noted that study designs vary between authorities, with some requiring full replicate studies and others accepting cross over studies instead. Acceptance criteria also differ, such as US utilizing the reference-scaled average bioequivalence (RSABE) approach meanwhile the EU and Canada apply the tightened 90% confidence interval.

Complex products face further divergent requirements. For inhalation products some regulators require clinical endpoint (CE) studies while others accept PK study along with in vitro analytical characterization methods. While US historically required CE studies for many generics of orally inhaled products, EU has moved toward accepting in vitro demonstrations of therapeutic equivalence, considering PK endpoints as valid surrogate markets for both efficacy and safety.

Peptide products, particularly those delivered via devices often have different requirements. For instance, the US may require additional data to determine whether risks are associated with the device itself impacting the clinical effect or safety profile. It was also noted that while region-specific PSGs offer companies more predictability for recommended studies, they can paradoxically limit flexibility in global development. Despite their technically nonbinding nature, where health authorities are expected to remain open to alternative methods of demonstrating bioequivalence with sufficient scientific rationale, companies report that these guidances often function as de facto requirements. This restricts their ability to design harmonized studies that comply with multiple regulatory frameworks simultaneously. This challenge was demonstrated, for example, by a PSG for a generic complex respiratory product where the US recommends two in vitro BE studies, one in vivo BE study with PK endpoints, and one comparative clinical endpoint BE study (with questionable scientific value) all with US RLD.

Population requirements for clinical studies

Beyond product-specific concerns, population requirements for clinical studies represent another significant barrier. Multiple sources noted the requirements for country-specific populations across numerous markets including Canada and Japan, and varying acceptance of studies with foreign populations. This necessitates recruiting specific demographic groups for studies that otherwise would be identical in design and purpose.

One company developing an ophthalmic product noted specific requirements for including patients with blue eyes for US clinical trials, potentially related to photosensitivity concerns. For biosimilars, companies historically faced requirements to include local populations, although some positive changes have occurred recently, with Japan removing its requirements for local population studies based on the characteristics of the pharmaceutical products, unless it is specifically suggested that there is a clinically significant ethnic difference between foreigners and Japanese.

Financial implications

The unnecessary requirement to perform BE studies in a specific country/region in order to obtain approval in that country/region have additional financial implications, separate from other clinical study requirements. As an example, companies reported that it costs approximately $1.5 million to perform BE studies in Europe compared to $250,000 in other countries for essentially identical protocols – a six-fold cost difference. While EU does not mandate that these studies be physically conducted within its territory, companies noted high costs associated with conducting studies that meet divergent regulatory standards.

For complex generics, these costs escalate dramatically, with estimates ranging from $5-10 million for development. The costs for inhalation products that sometime require clinical endpoint studies and adds 12 to 24 months to development timelines is between $20-35 million. In some

extreme cases, companies have invested hundreds of millions before canceling projects due to these requirements.

The cost barrier becomes even more prohibitive for biosimilars. One company described their experience developing an ophthalmic biosimilar where conducting a global clinical trial involving 600+ patients required to seek commercial partners to share the significant financial burden. This led them to pursue a more limited approach with a 200-patient study focused on a single market rather than a global development strategy with clear implications for patient access in those markets.

Impact on market entry decisions

The burden of multiple duplicate clinical trials directly impacts which markets companies choose to enter. One company described eliminating projects requiring high-cost BE studies in patients for specific oncology products. Another explained that when different requirements exist between the US and EU, they sometimes choose not to pursue both markets, particularly when the smaller market alone cannot justify the additional costs of repeating BE studies. This presents a particular challenge for orphan drugs – used to treat rare diseases – where limited market potential, as well as patient recruitment limitations, make additional clinical requirements especially burdensome. Companies stated that these products would be more feasible to develop if only PK trials were required to offset the costs.

Although, there are instances where regulatory flexibility has been demonstrated. In one case involving a respiratory product, Canadian authorities initially requested a biomarker study estimated at $20 million but after discussions accepted a PK study and additional lab work costing approximately $3 million. While this represents progress, the additional time required for these correspondences with regulators prohibited parallel US/Canadian development further delaying market access.

Several companies described scenarios where products that could benefit smaller markets are not developed due to the prohibitive costs of conducting additional region-specific studies. For products where patient recruitment is challenging or the potential market is small, the time spent for patient studies often makes development economically unfeasible.

Multiple companies pointed out a perceived inequity in the system: innovator companies can use the same clinical studies in dossiers approved across multiple markets, while generic and biosimilar companies face requirements for market-specific studies despite the reference/comparator product being the same across jurisdictions.

Progress towards harmonization

Despite these challenges, interviews revealed some progress towards harmonization. Several companies noted that regulatory authorities are increasingly aligning their approaches through PSGs. As mentioned earlier, the FDA's significant revision of over 800 PSGs in 2024 to align with ICH M13A guidelines represents a significant step towards harmonization. Japan has recently removed its requirement for including Japanese patients in biosimilar clinical trials and now accepts data generated in other ICH countries. The FDA has reduced requirements for demonstrating interchangeability of biosimilars, no longer requiring multiple switching studies.

However, challenges remain, especially regarding the need for harmonization of comparative efficacy study (CES) requirements for biosimilars. CES, traditionally considered a final confirmatory step after analytical and PK evaluations, are increasingly being reconsidered by stringent regulatory authorities such as the EMA, MHRA, and FDA (79). Notably, the FDA's 2025 draft guidance on biosimilars articulates a more definitive framework supporting the omission of CES when a comprehensive comparative analytical assessment, PK similarity, and immunogenicity evaluation sufficiently demonstrate biosimilarity (80). This updated guidance reflects the FDA's evolving scientific approach, recognizing that well-validated analytical and functional comparability data can obviate the need for CES in many cases. Additionally, ongoing

discussions continue regarding the use of PD biomarkers to further reduce clinical data burdens. Despite these advances, legislative and regulatory differences still influence expectations across jurisdictions, and significant barriers persist, underscoring the need for continued efforts toward global regulatory harmonization to improve patient access to affordable medicines.

II. Reference/comparator product requirements

The second most significant challenge for generic and biosimilar companies concerned reference/comparator product requirements. Companies revealed consistent issues related to obtaining appropriate reference products, navigating country-specific requirements, and managing the substantial challenges and costs associated with acquiring multiple reference products or reference lots for development.

Region-specific reference/comparator product requirements

A huge barrier exists in the requirements to use region-specific reference products as comparator products in different markets. Multiple companies reported that each regulatory authority typically requires BE studies to be conducted against locally sourced reference/comparator products even if the reference/comparator product is same across all countries. Companies explained that US reference/comparator products cannot be used for EU studies, as each region has very specific requirements. This creates a situation where companies must conduct essentially identical studies multiple times using different reference/comparator products.

The requirements extend beyond simple regulatory preference often stemming from statutory requirements. In the US, legislative requirements prohibit the use of foreign reference/comparator products for generic development, regardless of whether the products are identical. Companies noted that geographic acquisition rather than product composition often dictates acceptability, with them explaining that the products have to be purchased locally.

Reference/comparator product access barriers

Beyond regulatory requirements, physically obtaining reference/comparator products present significant challenges for certain product categories. Two particularly problematic categories emerged from company interviews:

REMS- protected products create substantial access barriers. Risk Evaluation and Mitigation Strategy (REMS) programs restrict distribution of certain medications with serious safety concerns. Multiple companies reported significant difficulties obtaining REMS-protected reference/comparator products for BE testing. The approval process for accessing REMS products is lengthy and susceptible to delays, with one company describing a process requiring product authorization filing with the FDA, followed by a 28-day review period and up to 120 days for Covered Product Authorization (CPA) approval. Companies also noted that innovator firms can employ various tactics to delay generic company's access to samples.

Orphan drugs present both access and cost barriers. Their limited production volumes and high prices make obtaining enough for BE testing prohibitively expensive. One company reported that for an injectable orphan drug product in the US, the costs of the US RLD made generic development economically unfeasible in what would otherwise be the most sustainable market, whereas the EU RLD was approximately 90% cheaper. However, regulatory restrictions prevent using the more affordable EU reference/comparator product for US development.

In addition to these categories, non-availability of reference/comparator product in some markets poses a significant barrier for being able to develop a generic/biosimilar medicine for those markets. In cases where foreign reference/comparator products are not acceptable the market is inaccessible for development through generic and biosimilar medicines approval pathway directly impacting patient access to these medicines in these regions.

Financial impact of reference/comparator products requirements

The financial burden of acquiring reference/comparator products constitutes a major barrier to global development, particularly for biosimilars. One company reported spending 100 million dollars for a US reference/comparator product alone, a staggering figure that dramatically impacts development economics. Another noted that biosimilar study costs often exceed those of originator studies, highlighting how current regulatory frameworks create financial disincentives for developing more affordable alternatives.

Price disparities between markets further complicates development. Price of reference/comparator products are heterogeneous, leading companies to prioritize acquisition of reference products from jurisdictions where the product is less expensive when possible. One company explained their approach of using reference/comparator products from certain jurisdictions for clinical studies due to cost-effectiveness compared to other jurisdictions and easier availability for bulk procurement in some regions.

These cost barriers directly impact market access. Companies reported abandoning development for certain markets when reference/comparator product costs could not be justified by the potential return on investment. This particularly affects smaller markets and medications for rare diseases, where limited patient populations already constrain commercial viability.

Additional studies for foreign-reference/comparator products

To address reference/comparator product challenges, many companies conduct analytical bridging studies to demonstrate equivalence between reference products from different regions. While this approach offers a potential pathway to reduce redundant clinical trials, it still imposes significant costs and development challenges when the reference/comparator products are identical and manufactured at the same site.

For biosimilars, analytical bridging has become standard practice but remains resource intensive. Companies must characterize multiple batches from different regions to establish comparability.

Companies explained that reference/comparator product usage in clinical studies is becoming harmonized across ICH countries, allowing reference products from only one ICH country to be used in clinical studies while CMC comparability is established through characterization of multiple batches sources from multiple countries.

Some markets impose particularly rigorous requirements for analytical bridging. One company noted Korean regulatory expectations for analytics against their reference/comparator product, requiring comparability on three batches initially, and if any irregularities are found, expanding to 6-10 batches and potentially a complete biosimilar panel. This demonstrates how analytical bridging can expand into extensive additional testing.

Progress in harmonization efforts

Companies have reported some positive developments in reference/comparator product requirements. The Access Consortium – including Australia, Canada, Singapore, Switzerland, and the UK – has made progress in accepting foreign comparator products for BE studies. Detailed review of Access countries' criteria for accepting foreign reference/comparator products demonstrates a growing recognition of the scientific validity of this approach.

As mentioned previously, in some jurisdictions, foreign reference/comparator product usage for biosimilars in clinical studies is acceptable. In some countries, this allows reference/comparator products from a single ICH country to be used in clinical studies while analytical comparability is established across multiple sourcing regions.

However, implementation challenges remain. Acceptance criteria still vary significantly between countries, creating a complex patchwork of requirements that companies must navigate. These varying criteria often depend on factors like dosage form, manufacturing site, and drug properties rather than evidence-based scientific principles.

III. Manufacturing and production

Generic and biosimilar companies revealed significant manufacturing and production challenges that further complicate the pursuit of single global development. Problems that arise during manufacturing and production are often interrelated with clinical trials and reference/comparator product issues, that together create additional barriers to efficient development and timely market access.

Regional manufacturing specifications and standards

Companies consistently reported facing divergent manufacturing specifications and quality standards across different regulatory jurisdictions. Despite products being identical in formulation, companies often need to establish different production parameters to satisfy varying regional requirements.

One of the most striking examples mentioned by companies involves the purity of the product, particularly for the Japanese market. Although in this section, the focus is on the manufacturing/process, the API purity impacts the development of the products leading to multiple rounds of purification beyond what is required in other markets. One company explained that this creates the need for separate manufacturing campaigns specifically for this market, increasing production complexity and costs.

Similar challenges exist in Brazil, where additional API validation criteria create extra costs to manufacture separate batches. Several companies noted that these additional requirements rarely contribute to meaningful quality or safety improvements but significantly impact manufacturing efficiency.

For biosimilars, one company described extensive CMC studies are required by different authorities, including impurity profiling, forced degradation testing, extractables and leachable analysis, virus validation, process characterization, and method validation. While each authority

requested similar studies, the specific parameters and acceptance criteria often differed, requiring customized approaches for each market.

Stability and packaging requirements

Climate zone considerations emerged as a significant manufacturing challenge across multiple companies. Different regions fall under contrasting stability testing zones based on their climate conditions – with the US is categorized as Zone II, and Southeast Asia and Central Africa fall under Zone IVb (hot and humid). These different stability requirements necessitate more robust packaging for products intended for hot and humid countries, affecting formulation decisions and increasing complexity in global supply chains.

Packaging configuration requirements also vary significantly. Some markets mandate specific packaging types, e.g., bottle vs blister, impacting development considerations like stability testing. These differences force companies to maintain multiple packaging lines and conduct separate stability studies for identical products. It was also noted that certain regulators such as the US require a DMF for packaging materials whereas others such as EU only require a certificate of analysis.

One company highlighted how stability requirements from Australia's TGA were more stringent than other regulated markets. The company was required to conduct additional time-out-of-refrigeration studies to establish shelf-life at room temperature and derive storage norms beyond standard refrigerated conditions. These requirements directly impact label claims, can affect marketing strategies and create additional manufacturing complexity.

Device-related manufacturing challenges

For combination products involving devices, manufacturing challenges become particularly complex. Several companies reported significant barriers related to device requirements across different markets. For inhalation products and injectable products with delivery devices,

companies face inconsistent regulatory expectations regarding device performance and compatibility testing.

One biosimilar company described a potentially “catastrophic” delay when the US requested redesign of a prefilled syringe for an ophthalmic product, despite the product being intended for healthcare professional administration only. This type of late-stage manufacturing change can significantly impact timelines and costs, especially when different authorities have conflicting device requirements.

Another company noted challenges with demonstrating BE for complex drug-device combination products in the US, given the requirements for reference/comparator product and generic sameness and mitigation of use-related errors. These requirements necessitate conducting extensive human factor studies, which add to the development costs and timelines. The complex interactions between device components and active ingredients create additional manufacturing challenges that vary across markets.

Facility inspections and compliance issues

Manufacturing facility inspections represent another barrier, with various companies reporting that health authorities conduct their own inspections of manufacturing facilities rather than relying on inspections performed by other regulators, creating redundancies and delays. One company specifically highlighted how when US manufacturing sites add new lines for smaller batches of products for ex-US markets with different specifications multiple health authorities require in-person inspections instead of relying on inspections conducted by other regulators causing significant delays in development and launch timelines. This redundancy leads to launch delays and increases operational complexity for companies.

One company noted that, in their experience, approximately 50% of Complete Response Letters (CRLs) in the US are now inspection-related, with re-inspection timelines extending beyond a

year with limited ability to meet with FDA post-inspection. These delays can extend approval timelines by six months or more, significantly impacting market access.

The rigorous nature of these inspections further complicates development, as noted by one company that the FDA inspections are making strict observations regarding API synthesis processes. This heightened scrutiny requires companies to allocate resources to ensure compliance with varying standards across authorities.

The increased reliance on Contract Manufacturing Organizations (CMOs) and Contract Development and Manufacturing Organizations (CDMOs) further complicates this landscape. Companies reported that CRLs linked to facility deficiencies at contract manufacturers can create backlogs affecting multiple applications tied to the same facility.

Different countries also maintain varying requirements of Qualified Person (QP) release or local release of drug products for market. As one company noted, several jurisdictions including the EU, Brazil, Canada, and Australia require country-specific release procedures rather than accepting testing and release via common approved laboratory.

Local manufacturing requirements

Some markets impose requirements for local manufacturing as part of national industrial policies. One biosimilar company explained that Russia, Saudi Arabia, Brazil, and Algeria require technology transfer to local entities to enable local manufacturing of drug substance, drug product, or packaging. These requirements aim to promote local industries and increase domestic capabilities but create significant challenges for companies pursuing global development strategies.

These local manufacturing mandates present particular difficulties for biosimilar companies, who may be reluctant to share intellectual property and trade secrets with commercial partners in emerging markets. This reluctance leads to selective market entry strategies, undermining the potential for truly global development approaches.

Batch size and post-approval requirements

Varying requirements for registration batch sizes further complicate global manufacturing strategies. One company noted that while standard and non-standard batch sizes are acceptable for US registration, China only accepts standard batch sizes. These differences force companies to produce specific batches solely for registration purposes in certain markets.

Post-approval regulatory requirements also differ significantly. As one company explained, for the US market, certain API percentage difference would not be considered under SUPAC (Scale-Up and Post-Approval Changes) guidance, whereas these differences would be considered in other markets. These inconsistencies create ongoing compliance challenges throughout the product lifecycle.

Financial implications of manufacturing variations

Several companies reported that the need to maintain separate manufacturing processes, conduct additional testing, and manage multiple supply chains with differing requirements significantly increases production costs. For biosimilars, one company indicated that development costs for regulated markets are 4-5 times higher than for semi-regulated markets due to stringent regulatory requirements.

The business case for developing products becomes particularly challenging for smaller markets and orphan drug products. One company explained that while certain products might be technically feasible to manufacture, the need for specialized productions for small markets makes them economically unviable. Without large markets to distribute fixed manufacturing costs, products may not be profitable enough to justify development.

For oral peptide products, multiple companies noted that API manufacturing is particularly expensive, with additional costs for absorption-enhancing excipients further complicating production economics. These manufacturing challenges combined with the clinical assessment

and reference/comparator product hurdles discussed previously can render development economically unfeasible for certain markets.

Progress and potential for harmonization and convergence

As noted in previous sections, advances in harmonization/convergence efforts, by some jurisdictions, have made significant progress in addressing CMC challenges by allowing the use of reference/comparator products from a single jurisdiction across multiple markets. This important development reduces the need for market-specific manufacturing processes and testing, streamlining global development. Similarly, the Access Consortium countries have made strides in accepting foreign reference/comparator products, further reducing divergent requirements related to manufacturing.

For biosimilars, the ability to use reference/comparator products from a single ICH country for clinical studies is very relevant, though analytical characterization across multiple batches is still required. The “totality of evidence" approach is increasingly accepted for addressing CMC differences, creating pathways for more rational harmonization.

Several international collaborative initiatives are making notable contributions to regulatory convergence (81). The ICMRA provides strategic coordination among regulatory authorities on shared challenges. The Pharmaceutical Inspection Co-operation Scheme (PIC/S) works to harmonize inspection procedures worldwide, with 54 participating authorities adopting a unified GMP (Good Manufacturing Practice) standard. The WHO’s International Collaboration on GMP Inspections initiative represents another promising advancement. This program enables participating regulatory authorities to rely on each other’s inspection outcomes through a collaborative assessment process. Major regulatory agencies including the EMA, ANSM (France), MHRA (UK), FDA, TGA (Australia), HC, and PMDA are participating in this pilot phase. Following the initial assessment period, authorities can utilize inspection reports, assessment

documentation, and compliance information from partner agencies to make regulatory decisions without conducting redundant inspections.

Despite these positive steps, significant challenges including differences in regulatory interpretation, varying requirements for local manufacturing, and inconsistent inspection protocols continue to fragment the global development landscape. Although harmonization initiatives show promise, the full convergence of manufacturing expectations across diverse global markets remains an ongoing challenge and much remains to be done to align global manufacturing expectations.

Overview of all Case Studies

Based on our primary and secondary research we identified 52 pharmaceutical products facing specific regulatory barriers that impede wide access to generic and biosimilar medicines, which span across four categories: simple generics (n=18), complex generics (n=17), biosimilars (n=8), and orphan drugs (n=9). Common regulatory challenges impacting ability of companies to develop generic and biosimilar medicines for global markets include need for redundant BE studies and other testing to meet statutory requirements (e.g., use of local reference/comparator products), inconsistent clinical study requirements and trial designs, reference/comparator product acquisition barriers, divergent quality specifications, and market-specific manufacturing requirements.

Table 4, illustrates the main case studies discussed in the following sections, highlighting the need for global alignment in regulatory requirements. For each category, we examine cases that demonstrate how these regulatory inconsistencies create barriers to global patient access. The complete list of all generic and biosimilar medicines identified during this research is provided in Supplementary Table 2.

Table 4. Example case studies. Tabulated are the example case studies for generics and biosimilars (column 1), key development barriers for each generic/biosimilar (column 2), region and year of first generic/biosimilar approval globally (column 3), region and year of subsequent generic/biosimilar approval in US, EU, Canada and Japan as applicable.

Active Pharmaceutical Ingredient	Key Development Barriers	First Generic/ Biosimilar Approval	Subsequent Approvals
Levothyroxine Sodium	TESTING REQUIREMENTS: o Market-specific dissolution testing methods o Rejection of standard USP methods by certain authorities REGULATORY INCONSISTENCY o Divergent biowaiver criteria for multiple strength products o Contradictory standards for dissolution testing methods	US 2002	EU 2009 Japan 2005 Canada 2023
Apixaban	BIOEQUIVALENCE METHODOLOGY: o Redundant BE study requirements across markets o Duplicate specialized administration studies REGULATORY INCONSISTENCY: o Inconsistent classification pathways o Divergent food effect assessment requirements	US 2019	EU 2020 Canada 2022
Teriparatide	IMPURITY REQUIREMENTS: o Divergent impurity profiling thresholds o Market-specific immunogenicity study requirements	EU 2016	Japan 2019 Canada 2020 US 2023
Liraglutide	REFERENCE/COMPARATOR PRODUCT REQUIREMENTS: o Lack of recognition of reference/comparator product equivalence across markets o Requirement for separate development against market-specific references/comparators DEVICE SPECIFICATIONS: o Divergent requirements for delivery device evaluation o Inconsistent approaches to alternative device design	US 2024	EU 2024
Ranibizumab	DEVICE SPECIFICATIONS: o Disparate regulatory approaches to device differences o Region-specific device redesign requirements INTELLECTUAL PROPERTY BARRIERS: o Overlapping patent protection barriers affecting development strategy	EU 2021	US 2021 Japan 2021 Canada 2022
Trastuzumab	REGULATORY INCONSISTENCY: o Divergent classification of hyaluronidase (active vs. excipient) o Patent barriers due to regulatory classification decisions	EU 2017	US 2017 Japan 2018 Canada 2019

	MANUFACTURING REQUIREMENTS: o Inconsistent GMP evaluation requirements		
Lenalidomide	REGULATORY INCONSISTENCY: o Divergent risk evaluation and mitigation requirements across jurisdictions REFERENCE/COMPARATOR PRODUCT ACCESSIBILITY: o High costs of reference/comparator product acquisition BIOEQUIVALENCE REDUNDANCY: o Market-specific BE study duplication	EU 2018	US 2021 Canada 2021 Japan 2023
Octreotide Acetate	BIOEQUIVALENCE METHODOLOGY: o Divergent interpretations of identical clinical data o Different acceptance criteria for BE parameters IMPURITY REQUIREMENTS: o Market-specific impurity acceptance thresholds o Inconsistent requirements for immunogenicity risk assessment	EU 2019	Canada 2020 US 2023

1. Simple generics case studies

We identified 18 simple generic products for which regulatory inconsistencies create barriers to global patient access. Nine of these medications (50%) appear on the WHO EML, underscoring their critical importance to global public health: levothyroxine sodium, darunavir, carbidopa/levodopa, enzalutamide, apixaban, dasatinib, everolimus, tacrolimus, and atorvastatin.

Cancer therapies represented the largest group, with seven products reported to have significant approval challenges in different jurisdictions. These oncology drugs face several distinct regulatory hurdles, for instance multiple and differing BE study requirements (e.g., fasting/fed vs only fasting or only fed, steady state two-way crossover vs multiple-dose cross over) emerged as the most common challenges affecting drugs like palbociclib, olaparib, and dasatinib. The financial implications were reported to be substantial, with many jurisdictions requiring BE studies with their local reference/comparator products, rather than accepting studies performed with reference products from other jurisdictions which often have the same formulation, trade dress

and are manufactured at the same site, and additional market-specific CMC requirements, effectively forcing companies to duplicate efforts across markets and limiting their ability to develop products for multiple markets.

Another prevalent issue was the variation in reference/comparator product strengths available across markets, impacting dasatinib and relugolix. For dasatinib specifically, separate BE studies are required for different strengths because reference/comparator products vary across countries. Study designs and acceptance criteria also differ between markets. While both the US and EU recommend two-way crossover studies, the EU product-specific guidance for dasatinib notes that if high intraindividual variability is expected, replicate study designs may be considered in line with relevant guidelines, while the US accepts full replicate design as an alternative. Meanwhile, lenvatinib faced different challenges with intellectual property landscape that created obstacles to developing single global formulations. Furthermore, companies reported that studies like nasogastric (NG) tube studies needed to be repeated for this drug in different markets (US and EU) even if the reference/comparator product is the same.

For widely used cardiovascular medications like rosuvastatin and atorvastatin, companies reported that separate BE studies must be conducted for different markets despite using identical reference/comparator products. Market-specific packaging requirements created additional complications, with HDPE bottles required for US markets versus blister packs for EU distribution. For anticoagulants like apixaban, companies must perform specialized clinical studies (i.e., separate NG tube studies) for US and EU markets, while also conducting separate BE testing across different jurisdictions with same reference/comparator product.

Transplant medications like everolimus, tacrolimus, and sirolimus faced particularly complex challenges. Companies encounter divergent impurity specification requirements. For example, tacrolimus has a 0.5% impurity acceptance threshold in the US versus 0.4% in China. BE testing

requirements also vary, with everolimus requiring different reference/comparator product strengths (10 mg for EU markets but 5 mg for US markets). Dissolution acceptance criteria similarly differ between regions, with variation in both percentage thresholds and required timeframes. Shelf-life calculations methodologies also vary significantly, with some regions calculating shelf-life from the finished product manufacturing date (US) while others use the premix manufacturing date (EU). Market-specific packaging count variations further complicate supply chain, with sirolimus requiring different unit counts per bottle for US versus China markets.

These variations in regulatory requirements directly impact patient access by increasing development costs, extending timelines, inefficient use of resources for redundant testing and in some cases, making certain markets commercially unviable for generic entry. The following sections examine representative case studies that exemplify these challenges in greater detail.

Case Study – Levothyroxine Sodium

Levothyroxine, a synthetic thyroid hormone used to treat hypothyroidism appears on the WHO EML and represents a critical medication for millions of patients globally. This case study demonstrates how contradicting biowaiver requirements for additional proportional strengths for oral solid dosage forms and lack of alignment with approaches accepted by regulators across markets could be prohibitive for development of these products from some markets.

Generic companies developing levothyroxine face significant challenges with dissolution testing requirements due to discrepancies between solubility and dissolution. As noted by companies, in vitro biowaiver requirements to waive additional strengths in Canada contradicts what is acceptable in EU where there are major differences in data requirements for low soluble drugs. Despite being highly soluble in acidic conditions and at pH 6.8, levothyroxine demonstrates poor dissolution without surfactants due to its low intrinsic dissolution rate. Canada, in general, allows use of justified amounts of surfactant to obtain meaningful dissolution (50-70% release) if sink

conditions cannot be achieved and surfactant levels for different strengths can also be varied to ensure same driving force, while EU does not accept the use of surfactants. However, in the case of levothyroxine, it was noted that HC did not accept the use of surfactant in media for biowaiver, as the solubility data suggested there is a sink although dissolution was incomplete. It was also noted that Canadian regulators expect that dissolution should be aligned with solubility results, along with the driving force concept, which led to rejected biowaiver applications in instances where the regulators asserted that sink is achievable without use of surfactant based on solubility.

Furthermore, while the US and EU accept testing multiple units per vessel to mimic the same driving force for comparative dissolution studies, Canada explicitly prohibits this approach significantly complicating required development for dissolution methodology. Additionally, comparison against reference/comparator product is not acceptable in Canada while this comparison is allowed in the EU to show similar dissolution.

Dissolution testing is particularly important for biowaivers, as levothyroxine comes in multiple strengths, making it essential for generic companies to be able to avoid multiple BE studies. It was however noted that BE studies are required by EU, as compared to US, for proportional similarity across different strengths of same drug product. These regulatory inconsistencies and denials of biowaiver applications that utilized approaches accepted in other jurisdictions illustrate how regional regulatory differences can significantly impact pharmaceutical development strategies despite established physicochemical properties of the drug.

This case study particularly highlights lack of alignment with approaches accepted by regulators across markets such as additional biostudies for non-biostrengths, single unit testing for in-/low-soluble products, dissolution testing requirements for additional proportional strengths, inconsistency in acceptance of surfactant usage and acceptance of comparison against comparator product, among others. Therefore, extensive in vitro data needs to be generated for

multiple regulators, and one data set is not enough for approval across multiple markets resulting in duplicative efforts for different markets.

Case Study – Apixaban

Apixaban, a direct oral anticoagulant used to prevent stroke in patients with atrial fibrillation and for treatment and prevention of venous thromboembolism, represents a critical medication on the WHO EML. This case illustrates how regulatory inconsistencies in BE study requirements necessitate redundant testing even when scientific rationale for divergence is minimal.

The primary issue for generic companies developing apixaban has been the need to conduct separate BE studies for different markets with their respective local reference/comparator product despite the reference product being the same. While both the FDA and EMA recognize Eliquis® as the reference/comparator product, they do not accept BE data from studies performed in jurisdictions other than their own owing to statutory requirements. This regulatory disconnect forces companies to duplicate studies with essentially identical protocols without ‘just cause’, substantially increasing development costs without apparent scientific justification.

Significant progress toward regulatory harmonization has been achieved through ICH M9 guidelines, which allow biowaivers for IR products classified as BCS class I (high solubility, high permeability) or class III (high solubility, low permeability) (82). Many authorities have adopted these guidelines, creating potential pathways to avoid unnecessary testing. However, apixaban highlights the limitations of current harmonization efforts since current solubility data does not allow definitive BCS classification for this compound (83). This regulatory uncertainty leaves companies in a position where they must continue conducting full BE studies.

A closer examination of regulatory guidance documents across jurisdictions also reveals subtle but important differences in regulatory approaches. While both FDA and EMA require BE testing on the 5 mg strength with potential waivers for the 2.5 mg strength, the EMA guidance suggests

a possible BCS-based biowaiver pathways if the applicant generates sufficient solubility data to classify apixaban as a BCS class III drug (83,84). The FDA guidance makes no mention of this alternative pathway, demonstrating a regional disparity in development options.

Beyond standard BE testing, companies must also conduct specialized clinical studies for different administration routes. FDA guidance explicitly requires in vitro feeding tube studies for NG tube administration using specific parameters. These specialized studies need to be repeated for different markets despite identical reference/comparator products and established testing protocols.

These duplicative requirements directly impact development resources, with each additional BE study adding substantial costs and time to development programs. For medications like apixaban that serve patients with life-threatening conditions, these delays can have significant public health implications. The situation becomes particularly problematic in smaller markets where the additional development investment may not be commercially justified, potentially limiting access for patients in those regions.

2. Complex generics case studies

Complex generic medications present additional regulatory challenges due to their specialized delivery systems, intricate formulations, or unique manufacturing processes. The US FDA defines these products as generics with complex active ingredients, formulations, routes of administration, or dosage forms, while the EU categorizes many of these as ‘hybrid medicines’ that cannot rely on simple BE to demonstrate equivalence to reference/comparator products. Other jurisdictions do not have a separate classification for these generics. Our investigation identified 17 complex generic products facing significant regulatory inconsistencies across markets.

Notably, eight of these medications (47%) appear on the WHO EML, underscoring their critical importance to global health: nab-paclitaxel, paliperidone palmitate, risperidone long-acting injectable, albuterol sulfate, tiotropium bromide, fluticasone furoate/vilanterol, fluticasone propionate, and budesonide/formoterol fumarate. This high proportion of essential medicines highlights the urgent need for regulatory alignment to ensure global access to these critical therapies.

Nanoparticle-based formulations and nanosuspensions face particularly challenging regulatory environments. For nab-paclitaxel, an albumin nanoparticle formulation used in metastatic breast cancer, non-small cell lung cancer, and pancreatic cancer, companies reported inconsistent expectations for particle size distribution analytics and stability requirements across jurisdictions. Evolving PSG and review standards were particularly noted as a challenge by companies. Specifically, they reported significant delays in the US approval process, with some generics receiving US approval approximately 6 years after the same product has already been approved in Canada and EU. Similarly, paliperidone palmitate, a nanocrystal suspension for schizophrenia treatment, encounters divergent approaches to demonstrating BE, with some markets requiring full clinical trials while others accept PK studies with appropriate in vitro characterization and alternative model-integrated approaches. Differences in the dissolution specifications and acceptance criteria for device design differences for US and EU were also noted.

Long-acting injectable microsphere formulations present another category with substantial cross-market inconsistencies. Risperidone, formulated within microspheres for long release, used for psychiatric conditions, faces divergent approaches to establishing equivalence. Companies reported one jurisdiction requiring demonstration of microsphere morphology throughout shelf-life while another focused on drug release profiles. These differences lead to entirely separate stability programs for different markets, significantly increasing development costs.

In addition to requirements for establishing BE to local reference/comparator product and repeated characterizations for each jurisdiction, peptide products encounter challenges with varied regulatory approaches to impurity control and characterization, and immunogenicity assessments- discussed in detail in the case study below. Teriparatide, liraglutide, semaglutide, tirzepatide, and exenatide all require market-specific approaches to impurity qualification, with companies reporting that even minor differences in regulatory expectations require separate development pathways.

Inhalation products for respiratory conditions represent one of the most challenging complex generic categories. Market specific regulatory requirements and increasing costs impacts development of inhalational products for multiple markets. Products like fluticasone propionate/salmeterol, albuterol sulfate, tiotropium bromide, and other asthma/COPD medications encounter highly variable regulatory approaches to demonstrating equivalence. Companies reported significant differences in required in vitro testing parameters, clinical endpoint studies, and device specifications. Additional challenges noted include: divergence in PK study requirements for proportional dose (i.e., highest strength for Canada vs all strengths for US); varying acceptance of foreign reference/comparator products and analytical requirements for BE studies; requirement for additional region-specific studies (such as PK study and lab work) to establish BE; requirement for process validation prior to approval (i.e. EU requires this whereas US does not); varying acceptance level for alternate/in vitro approaches; and high-level of uncertainty with regulatory approaches across jurisdictions with shift to greener propellants.

For injectables, pressurized metered-dose inhalers and other drug device combination products, different markets apply inconsistent standards for demonstrating device equivalence, with some requiring identical devices while others focus on comparative performance and jurisdictions like EU have been noted to rely on adherence with International Organization for Standardization (ISO) 13485, labeling and training to mitigate any differences between devices for some products.

A lack of harmonized device acceptance criteria (such as Code of Federal Regulations (CFR), Conformité Européenne (CE) certification, ISO compliance) across jurisdictions was also noted.

These regulatory divergences have particularly profound impacts on complex generics, where development costs are already substantially higher than simple oral solid dosage forms. In many cases, companies reported completely abandoning development for certain markets due to their inability to harmonize development programs. The following case studies examine some of these challenges in greater detail, in addition to what is shown in Table 4.

Case Study – Teriparatide

Teriparatide, a recombinant form of parathyroid hormone used for osteoporosis treatment, illustrates the challenges companies face when navigating inconsistent requirements across jurisdictions, particularly regarding impurity profiling and immunogenicity assessments. A fundamental regulatory inconsistency begins with the very classification of the product. While the FDA categorizes teriparatide biosimilar products as complex generics, the EMA, HC and PMDA classify them as biosimilar. This difference in categorization immediately places companies on different regulatory pathways with distinct requirements and expectations, complicating global development strategies.

The most significant regulatory inconsistency involves different approaches to impurity evaluation noted by companies. Canadian regulators, aligned with European standards, apply reporting thresholds of 0.1%, identification thresholds of 0.5%, and qualification thresholds of 1.0% for peptide-related impurities. In contrast, the FDA applies more stringent requirements, with identification thresholds of 0.1% and expectations that each peptide-related impurity level in a generic product must be the same as or lower than found in the RLD. Additionally, FDA requires that any new specified peptide-related impurity must not exceed 0.5% and must be characterized and justified as not affecting safety or effectiveness.

Regulatory progress has occurred in some areas. FDA's August 2024 PSG for teriparatide allows for waiver of in vivo BE studies if the generic product is qualitatively (Q1) and quantitatively (Q2) the same as the reference/comparator product (85). This approach acknowledges that for certain parenteral solutions, BE can be self-evident under specific conditions. However, this streamlining applies primarily to the BE aspect while impurity and immunogenicity requirements remain stringent.

The immunogenicity assessment requirements represent a stark divergence, where HC does not require immunogenicity studies for teriparatide while FDA might need both adaptive and innate immunogenicity studies. These are complex and costly assessments that significantly extend development timelines. One company opined that the product had been successfully marketed in Europe for several years while still facing regulatory hurdles in the US, noting that European regulators considered a brief discussion on potential immunogenic responses sufficient. Challenges with evolving review standards where US regulators require additional immunogenicity testing with different controls than previously directed, adding several months to development timelines and costs, was also noted.

Companies described immunogenicity assessments as a "black hole", noting that even specialized third-party laboratories struggle to meet shifting expectations regarding cell types and study populations with regulatory inconsistency not only between regions but also with evolving approaches within individual agencies over time.

Case Study – Liraglutide

Another complex generic facing significant market-specific development barriers is liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist used for type 2 diabetes and weight management. Companies encountered multiple challenges when developing generic versions of this medication, beginning with the requirement for separate, full development programs against

each country's local reference/comparator drug, despite the reference being demonstrably identical.

As noted above for prior case studies, companies reported certain jurisdictions require separate development against the market-specific reference/comparator product, for instance US regulators do not accept European reference data and vice-versa, necessitating repeated characterization with identical reference/comparator products. Companies noted that often the reference/comparator products in multiple jurisdictions are manufactured at one site and absence of manufacturing site information on product labels in many countries, makes it difficult for companies to provide evidence of reference/comparator product sameness across geographies. It was noted that in these instances bridging studies could be performed, similar to what is accepted for reference/comparator products for biosimilars, to demonstrate product sameness across multiple jurisdictions rather than conducting entirely separate BE studies.

Regulatory requirements for liraglutide generic products were recognized to vary across markets. For instance, the FDA requires extensive characterization with multiple orthogonal techniques, while European regulators accept BE studies as the primary basis for approval. However, like with teriparatide, and other peptides, the FDA provides PSG which allows waiver of in vivo BE if generic products meet the Q1 and Q2 requirements (86), allowing for a simplified development for generic companies.

Furthermore, companies raised similar concerns like with teriparatide. For instance, impurity identification and qualification thresholds differ significantly, with US identification threshold for unknown impurities being much more stringent than European thresholds. This forces companies to develop region-specific analytical methods and specifications, leading to increased costs.

In addition to drug-specific development challenges, the device component of liraglutide also faces challenges during development. There are differences in the device evaluation across

regions; European authorities rely on compliance with ISO standards and place greater emphasis on labeling and training to mitigate device differences, while US authorities apply a more prescriptive approach. The FDA guidance recommends that applicants examine the following: size and shape, external critical design attributes, and external operating principles of the reference device.

When patents on the reference/comparator product device necessitate alternative designs, companies face varying challenges with demonstrating equivalence. One company reported significant challenges with Comparative Use Human Factors (CUHF) study requirements requested by the US regulators while developing alternative device design even when the proposed design was widely used for other injectables with established patient and provider familiarity.

These regulatory inconsistencies have significant implications for patient access, particularly given the increasing demand for GLP-1 receptor agonists and periodic shortages of approved products. One company noted that while ANDA applications for liraglutide remained under extended regulatory review, patients were seeking unapproved sources of similar medications from online vendors and compounding pharmacies, potentially compromising patient safety.

3. Biosimilars case studies

While high volumes and market prices make business cases stronger for highly regulated markets (US, EU, Japan), high development costs (4-5X higher than semi-regulated markets) and complex intellectual property related issues make it less attractive for smaller/ emerging companies. Biosimilar development is very complex requiring at least $70-80M in investments and >6 years for global development. Single global development is an ideal scenario for biosimilars given the high-cost investment but not achievable due to varying regulatory requirements across markets. Additionally, the complexity and sophisticated manufacturing processes of biologic medicines

create unique regulatory challenges. Biosimilar developers walk a tight rope with the ever-changing regulatory landscape. Our analysis uncovered eight biosimilar products confronting divergent approval pathways across international markets. Four of these biologics, including adalimumab, trastuzumab, etanercept, and infliximab, appear on the WHO EML, reflecting their importance in treating conditions affecting millions of patients worldwide.

Given high cost of development for biosimilars compared to generic medicine, companies positively noted advances in harmonization efforts in biosimilar development, such as acceptance of bridging studies for certain products, where data from animal and certain clinical studies using a foreign reference/comparator product can be used to establish an acceptable bridge to local reference product, by US and EU regulators to demonstrate biosimilarity (87). While these harmonization efforts are a step in the right direction, several challenges still remain with differing regulatory approaches across jurisdictions.

General challenges noted for biosimilar development include requirement to use local reference/comparator product to demonstrate clinical equivalence and/or for CMC requirements which increases cost of acquisition of reference products in certain markets and is impacted by unavailability of comparator product in certain markets. There is also a need for inclusion of local patient population in clinical studies by several regulators in LATAM, MENA and SEA. Additional complexities include different formulations and presentations of products - strengths (25mg vs 50mg), self-administered vs hospital administered, route of administration differences, device design differences, patent workaround - in different markets. Human factor study requirements for drug-device combination products in the US and EU are complex and cost/time intensive and are not required by LATAM, MENA and SEA. While totality of evidence is fast becoming the norm to explain underlying differences (e.g., batch to batch variation impacting glycosylation), there remains a disparity in what regulators are looking for and their background understandings.

For antibody-based immunological therapies, like etanercept, patent barriers create market access roadblocks that persist beyond regulatory clearance. The US market exemplifies this challenge, where layered intellectual property protections can postpone availability for years after authorization in other regions. Monoclonal antibodies used in oncology, including trastuzumab, pertuzumab, and ipilimumab, face varying clinical trials demands across jurisdictions. These products require separate development paths despite identical therapeutic goals, with some authorities, such as in EU, mandating substantially larger study populations with narrow therapeutic windows.

Delivery system disparities particularly affect ophthalmic treatments like ranibizumab and aflibercept. Regulatory bodies impose conflicting standards for device components and visual indicators, forcing companies to create market-specific designs, despite equivalent clinical performance, leading to extended development timelines without patient benefit. Differing regulatory approaches where certain products such as Hyaluronidase have been regulated as active substance requiring biosimilarity in the US, whereas EU sees it as excipient, requiring different development strategy across markets by companies- as detailed in the case study below.

Divergence in regulatory expectations for the development and approval of biosimilars is seen across all stages of development and implementation and another challenge noted by a company was approval of different fill volumes of biosimilar than that of the reference/comparator in the US which can slow down the launch and delay patient access.

The financial impact of these regulatory discrepancies falls heavily on biosimilars, whose development costs already reach nine figures. Companies frequently withdraw from certain markets when redesign or patent requirements become economically unfeasible, as examined in the following case studies.

Case Study - Ranibizumab

Ranibizumab, a vascular endothelial growth factor (VEGF) inhibitor used to treat various retinal conditions including age-related macular degeneration and diabetic macular edema, exemplifies how device-related regulatory inconsistencies create significant barriers to global access for ophthalmic biosimilars. This case highlights how variations in regulatory approaches to delivery systems (device components of the product) can delay or even prevent patient access to affordable treatment options.

The primary regulatory challenge for ranibizumab biosimilars centers on delivery device specifications. Companies reported developing pre-filled syringes with innovative features to ensure accurate dosing while navigating reference/comparator product patent protections such as tactile feedback mechanism when the correct dose is reached and modified marker lines. It was noted that the regulatory approaches to these device differences varied dramatically across jurisdictions. While European regulators focused primarily on demonstrating that the device delivers the medication accurately and safely, the device differences were not acceptable in the US despite the fact that Ranibizumab is exclusively administered by ophthalmic healthcare professionals, not patients, and 100% accurate dosing was demonstrated through comprehensive CUHF studies. US biosimilar regulations require the drug to be “highly similar with no clinically meaningful difference” but do not mandate identical delivery devices.

The implications of these divergent regulatory approaches are profound. Companies report that redesigning the pre-filled syringe would require approximately two years of development work, substantially delaying US market entry. This creates a scenario where the product could be approved and available to patients in Europe while remaining inaccessible in the US, despite containing the identical active ingredient. The economic consequences are equally significant, where it was noted that companies may abandon the US market entirely due to the prohibitive costs of device redesign, particularly considering that reference/comparator product patents on

certain device components would likely expire within the redesign timeline. This situation forces companies to choose between developing market-specific devices at a considerable expense or limiting product development to regions with more flexible device requirements, thereby impacting patient access in those regions.

This case demonstrates how regulatory inconsistencies related to delivery devices and not substantiated by scientific rationale create barriers to patient access. When companies need to develop alternative device designs for various reasons, including market-specific requirements, they face divergent regulatory approaches to evaluating these alternatives. While European regulators focus primarily on the accuracy and safety of the device, other jurisdictions may have more rigid requirements regarding similarity, despite identical active ingredients and demonstrated clinical performance. A more harmonized approach to evaluating delivery device modifications would enable broader patient access while maintaining safety standards. In addition to these regulatory challenges, it is worth mentioning that patent thickets represent an additional layer of complexity, particularly in the US market. In the case of ranibizumab biosimilars, these patent barriers encompass not only the drug but extend to the delivery system component and sterilization processes.

Case Study – Trastuzumab

The monoclonal antibody, trastuzumab, which targets HER2-positive breast cancer, represents a critical therapy on the WHO EML. This case illustrates how inconsistent regulatory approaches can create barriers to global patient access for life-saving oncology treatments.

Trastuzumab was initially approved as an intravenous (IV) formulation but has since been developed as a subcutaneous (SC) injection, providing clinicians and patients with treatment options that maintain equivalent pharmacological and clinical profiles. The SC formulation offers significant advantages for certain patients, including reduced administration time, less burden on

healthcare facilities, and more convenient administration method for patients (88,89). Studies comparing IV with SC trastuzumab indicate that each formulation offers unique benefits depending on individual patient needs and healthcare settings.

Companies report several challenges related to different regulatory oversight for GMP requirements. It was noted that many National Regulatory Authorities (NRAs) lack qualified resources to efficiently evaluate biosimilars, creating a problem that requires lengthy capacity-building processes. Additionally, it was noted that these authorities often do not rely on assessments already conducted by other regulatory bodies that have previously evaluated the same biosimilars, resulting in duplicated work. Companies also cite insufficient pharmacovigilance monitoring to assess the safety and efficacy of biosimilar interchangeability across jurisdictions.

Beyond these general challenges, the subcutaneous formulation of trastuzumab faces a specific regulatory inconsistency regarding hyaluronidase, an enzyme added to facilitate absorption. Regulatory authorities have different approaches to classifying this component. The FDA classifies hyaluronidase as an active substance that requires demonstration of biosimilarity to the reference/comparator product's version. This classification creates a significant barrier as the hyaluronidase used in the reference/comparator is patent protected, blocking development of the SC formulation in the US market. In contrast, EMA considers hyaluronidase an excipient rather than an active substance. This allows developers to use alternative sources for hyaluronidase or different approaches to subcutaneous delivery while maintaining the same clinical profile for the monoclonal antibody.

The consequence of variations in classification of hyaluronidase limits patients access to SC trastuzumab in the US versus Europe. Due to patent protection of hyaluronidase, US patients'

only option are to pay higher prices for the branded SC formulation or use the IV formulation at the cost of convenience.

This case highlights how both regulatory inconsistencies and specific technical classification decisions can have far-reaching implications for patient care and healthcare systems. Despite trastuzumab's status as an essential medicine for treating HER2- positive breast cancer, these divergent regulatory approaches often lead to differences in development to cater to certain markets, increasing costs and limiting availability across markets.

4. Orphan drugs case studies

Orphan drugs, designed to treat rare diseases affecting small patient populations, face unique regulatory and development challenges that are further complicated by inconsistent global requirements. Regulatory frameworks for orphan drugs vary considerably. US Orphan Drug Act defines rare diseases as affecting fewer than 200,000 Americans, EU's Committee for Orphan Medicinal Products (COMP) considers conditions affecting no more than 5 in 10,000 people, and Japan's PMDA designation is less than 50,000 people (90,91). From interviews with various generic companies, nine orphan drugs demonstrating several inconsistent regulations across jurisdictions were identified. Notably, three of these medications (33%) appear on the WHO EML: lenalidomide, octreotide acetate LAR depot, and glatiramer acetate. Although these therapies are limited to a small patient population, it is still essential to address these regulatory barriers.

Orphan drugs face particularly challenging economic considerations due to their limited market size, making regulatory inefficiencies especially damaging to development prospects. For these products, companies reported that redundant testing requirements with local references/comparators, inconsistent reference product standards, and market-specific clinical study demands frequently render development economically unfeasible for certain regions. Unlike conventional medications, where larger patient populations can offset development costs, generic

or biosimilar orphan drugs operate with razor-thin margins that leave little room for regulatory redundancies. Companies consistently reported that business cases for orphan generic development collapse under the weight of region-specific requirements, leaving patients in certain markets without access to affordable treatment options.

Cancer therapeutics represented a significant portion of the orphan drugs in our investigation. Targeted cancer therapies like niraparib, rucaparib, and dabrafenib, require clinical equivalence studies for each jurisdiction with respective local reference/comparator product and sometimes in local patient population which are prohibitively expensive, leading companies to abandon development in certain markets. Other cancer therapies like ixazomib face challenges due to high reference/comparator product costs, prompting selective market approaches based on regulatory burden. For instance, companies reported not pursuing EU approval for ixazomib since requirements were deemed too taxing compared to potential returns. Medications for pulmonary arterial hypertension like macitentan experience similar issues, with high cost of reference/comparator product, difficulty with acquiring the reference product and multiple batches because it is an orphan drug making studies across all markets economically unfeasible. One company also noted that the high cost of the US RLD for an injectable orphan drug product was prohibitive for developing a generic in the US.

For biologics like eculizumab, which treat rare blood disorders, companies reported difficulties in development because the reference/comparator product is limited to certain markets, making it challenging to pursue generic development for global markets. As noted previously, complex peptide products face significant regulatory divergence. For instance, for generics of glatiramer acetate, the US accepts comprehensive in vitro characterization studies while Canada and EU require full clinical studies in multiple sclerosis patients that can take approximately 8 years to complete. Companies noted that the limited number of eligible patients in these regions makes such studies particularly difficult to conduct. Difference in guidelines have profound impact,

particularly for orphan drugs, where development costs must be carefully balanced against limited market potential. In many cases, generic companies reported completely abandoning development for certain markets due to their inability to harmonize development programs, creating significant challenges with access to treatment for rare diseases. The following case studies examine some of these challenges in greater detail.

Case Study – Lenalidomide

Lenalidomide, an immunomodulatory drug critical for treating multiple myeloma, myelodysplatic syndrome, and mantle cell lymphoma, illustrates how divergent risk management requirements and regulatory standards complicate global development of orphan drugs. As a medication on the WHO EML, lenalidomide plays a vital role in global cancer treatment, yet companies face significant challenges in developing generic versions for multiple markets.

A primary challenge reported by companies involved inconsistent approaches to risk management plans across jurisdictions and burdensome study requirements for EU. Lenalidomide requires stringent monitoring due to its teratogenic potential (92), yet the specific requirements for risk evaluation and mitigation strategies vary considerably between markets. These differences necessitate region-specific implementation strategies that complicate global development plans. Companies noted that harmonized approaches to risk management would enable more efficient development while maintaining patient safety. Additionally, one company noted that the additional REMS requirements and challenges with acquiring reference/comparator products due to obstacles from innovator companies, including additional fee (20%-25%), delayed their development by 6-9 months.

Economic feasibility presents another significant barrier. Companies reported that the high costs of acquiring reference/comparator products for conducting comparative studies across all intended markets poses a substantial challenge, particularly given lenalidomide’s orphan status

and correspondingly high price point. They also noted that the drop in drug price by 90% within 2 months of market entry makes it hard for companies to mitigate cost of bringing the drug to market. This is a common issue faced by orphan drug products. This creates a situation where development becomes economically viable only in larger markets that can support the investment required, leaving smaller markets without access to more affordable options.

In addition to high costs of reference/comparator products, companies also experience market-specific studies. Despite reference/comparator products manufactured in the same site for global distribution, making product differences across regions negligible, companies must still repeat BE or comparative studies for each market-specific reference/comparator product.

The inconsistent approaches in monitoring and risk managements requirements, coupled with high costs and redundant clinical studies, adds substantial complexity to global development strategies, particularly for smaller companies with limited regulatory resources.

Case Study – Octreotide Acetate LAR

Octreotide acetate long-acting release (LAR) depot is designated as an orphan drug for acromegaly and is also used to treat symptoms associated with metastatic carcinoid tumors and VIP-secreting tumors. This complex peptide formulation faces divergent approaches to demonstrating BE and impurity control that substantially complicate global development.

Companies reported encountering different review experiences of having the same products – manufactured in the same facilities, submitted with identical data demonstrating BE, safety, and quality - resulting in divergent regulatory outcomes across different jurisdictions. For instance, one company described submitting its study results to both EU and US regulators where the Area Under the Curve (AUC) and maximum plasma concentration (Cmax) parameters was narrowly out of range. The data was submitted as a secondary endpoint which in early release timepoints were clinically insignificant. The company noted that while the EU regulators initially did not accept

their data, they took a lenient approach after meeting with them and approved the product, however the US regulators took a more stringent approach and required additional clinical BE studies. Companies acknowledge regulatory authorities' need to conduct independent assessment but expressed concern about significantly different outcomes from two major regulators evaluating identical products and data. They emphasized the need for early and open communications with regulators to address concerns, which is even more critical in cases where PSGs do not exist or is a draft.

Furthermore, differences in impurity and immunogenicity acceptance across jurisdictions, as previously noted for the other peptide products in the complex generic section, are also identified here. This case further demonstrates how technically identical products can face dramatically different approval outcomes across jurisdictions. As an essential medicine on the WHO list, these divergent regulatory reviews and requirements preclude patient's access to critical medicines such as octreotide across several regions worldwide.

Conclusions, Recommendations, Next Steps

This study has identified significant regulatory barriers that impede efficient global development of generic and biosimilar medicines. From >50 stakeholder interactions (interviews, reports, questionnaires), which included companies and independent subject matter experts, and our secondary research, we uncovered a complex landscape of regulatory divergence that creates substantial challenges for companies attempting to develop affordable alternatives to branded medications for a global market. The three most significant hurdles – clinical assessment requirements, reference/comparator product requirements, and manufacturing standards – along with others collectively create a fragmented and challenging development environment that increases costs, extends timelines, and ultimately restricts patient access to affordable medicines.

The financial and operational impact of these regulatory inconsistencies are profound. Companies reported investing hundreds of millions of dollars in duplicate studies that add little scientific value, facing tremendous cost differences for BE studies across regions, and making difficult market entry decisions based on regulatory burdens rather than patient needs. These challenges disproportionately affect development of treatments for small markets and rare diseases.

Our findings highlight several priority areas where a more harmonized global regulatory framework would greatly benefit patients and healthcare systems, and enable industry to bring more safe and effective generic and biosimilar medicines to market. Based on our comprehensive analysis, we identify four key areas where near-term harmonization efforts could yield substantial impact:

Establish legislative and regulatory pathways to allow use of foreign comparator products. This could reduce development costs substantially while maintaining appropriate scientific standards for establishing BE. The Access Consortium's progress in accepting the use of reference/comparator products from other regions demonstrates the feasibility of such approaches. This approach is further supported by the growing acceptance by major regulatory authorities (FDA, EU regulatory network PMDA) of reference/comparator product bridging studies for biosimilar development, allowing the use of foreign reference/comparator products for certain studies while establishing analytical comparability with local reference/comparator products.

Align technical standards across regulatory agencies.

Harmonization is urgently needed for dissolution testing methodologies, impurity thresholds, and manufacturing specifications. Regulatory discrepancies without scientific rationale should be eliminated. While ICH harmonization efforts provide a foundation, more rapid implementation and greater flexibility in benefit-risk assessments are essential. Companies have emphasized that regulators should consider not only safety risks but also the risk that patients may lack access to affordable medicines when brand-name drugs remain prohibitively expensive without generic alternatives.

Streamline development pathways for complex products and biosimilars.

Companies and regulators increasingly recognize that CES do not provide additional evidence of biosimilarity beyond what is established through comprehensive analytical assessments and clinical PK studies. Recent regulatory draft guidance by the FDA, along with publications from regulatory authorities in the EU, US, Japan, and the UK, as well as industry experts, consistently support the elimination of redundant CES when sufficient analytical and clinical PK data exist, highlighting this approach as a means to accelerate patient access to biosimilars (50,80,93–100). Many advances to allow biowaivers such as bypassing the need for in vivo BE studies have been introduced by the ICH M9 and M13 series. It is acknowledged that future M13 guidelines are in development to address biowaivers for additional strengths, however these are only limited to IR oral dosage forms. Given these advances, the ICH has recently approved the development of a new multidisciplinary guideline addressing factors to consider when determining the utility of CES in biosimilar development. Significant progress has been made for complex generic drugs through the FDA's Office of Generic Drugs (OGD) via the GDUFA Science and Research Program, which has established collaborations between the FDA, generic drug industry, and academia to promote innovation in quantitative methods and modeling (101,102). These model-integrated evidence approaches for virtual BE simulation, when combined with in vitro testing, offer promising alternatives to conventional in vivo studies. Global concurrence on these alternate approaches would help eliminate redundancy and pave way for efficient development pathways for generics and biosimilar.

Enhance regulatory collaboration.

Enhanced collaboration through work-sharing initiatives, harmonized regulatory approaches which are science-backed, and mutual recognition of these harmonized approaches would reduce redundancies and inconsistencies. A model similar to the EU's centralized procedure, where a single assessment is accepted by all 27 Member States, could serve as a template for broader international cooperation. Additionally, the EMA's OPEN framework facilitates parallel scientific

evaluations with non-EU regulators such as HC, TGA, ANVISA, and PMDA, enabling independent yet collaborative assessments that share expertise and promote regulatory harmonization. Consider expanding existing programs and initiatives such as Access Consortiums, the FDA-EMA Parallel Scientific Advice Pilot Program to include other major countries such as Japan, Canada, Australia, UK.

Limited or lack of access to essential medicines remains a critical unmet medical need in many countries, with direct consequences for patient health and outcomes. The urgency for regulatory harmonization cannot be overstated. Every day that passes with fragmented regulatory requirements directly translates to patients being denied access to affordable, life-saving medicines. Our research has identified 52 pharmaceutical products where regulatory inconsistencies have created barriers to patient access, including treatments for cancer, chronic diseases, and rare conditions. These are not merely theoretical or administrative concerns, but they represent real human impact, with patients in certain regions unable to access medications that are readily available elsewhere. The economic burden of healthcare costs continues to rise globally, making efficient development of affordable alternatives not just beneficial but essential. While complete regulatory alignment is not easily achievable due to several legislative barriers, targeted harmonization in the critical areas identified in this report, while maintaining robust safety and efficacy standards, should be treated as an urgent global health priority.

As stated by one of the interviewees, “Can a single dossier support access to more patients in more markets?” The research described herein reveals that this could be achievable within scientific reasons. The evolution toward single global development for generic and biosimilar products will require sustained collaboration between industry stakeholders and regulatory authorities. Technology, scientific understanding, and regulatory frameworks – what is now required is enhanced international cooperation and collaboration to translate these opportunities into tangible benefits for patients worldwide.

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