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

Collaborative project between University of Maryland and University of Michigan

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INTERNATIONAL GENERIC AND
BIOSIMILAR MEDICINES ASSOCIATION

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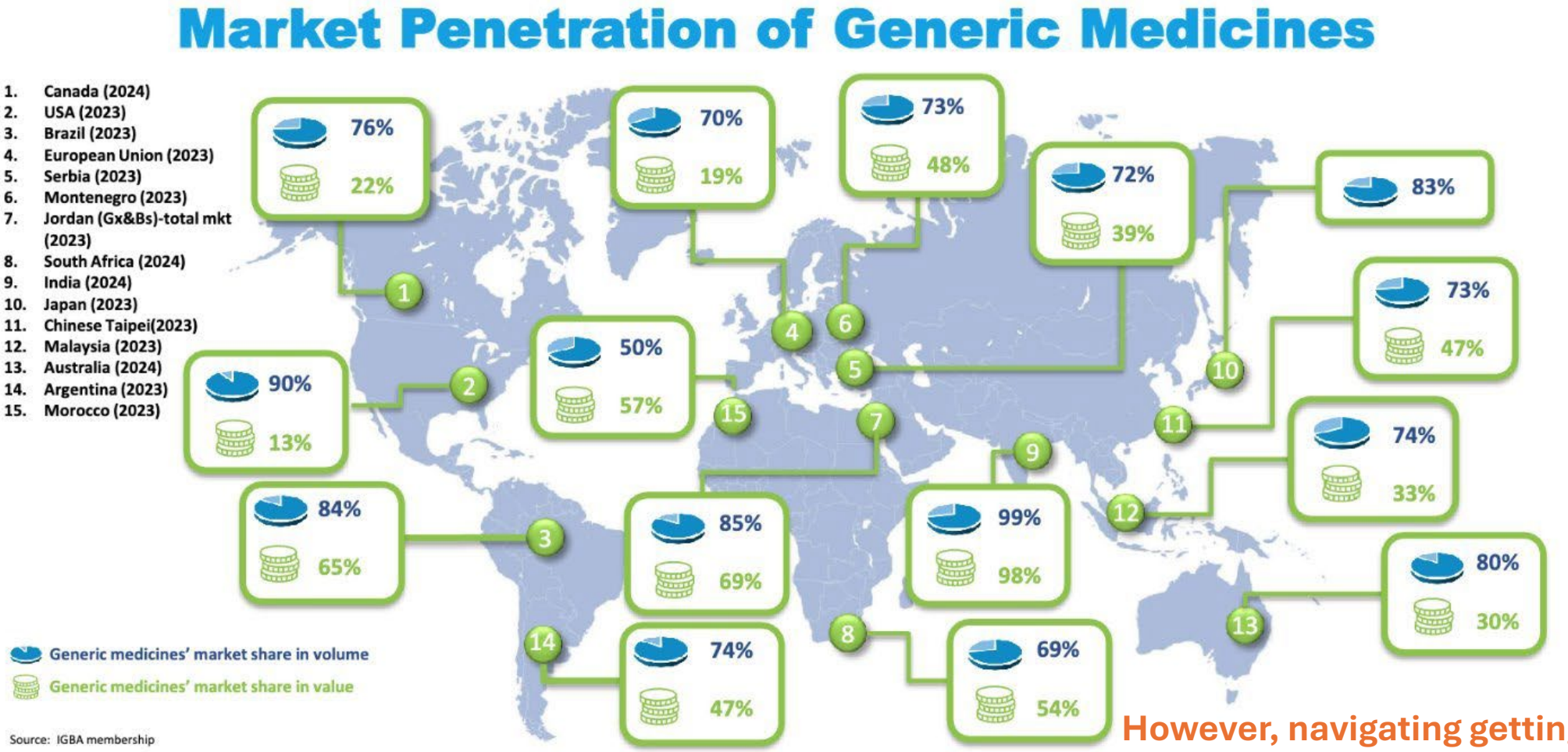
Generics and biosimilar medicines have extensive impacts on global markets



However, navigating getting approval for generics and biosimilars across different markets can pose challenges -->

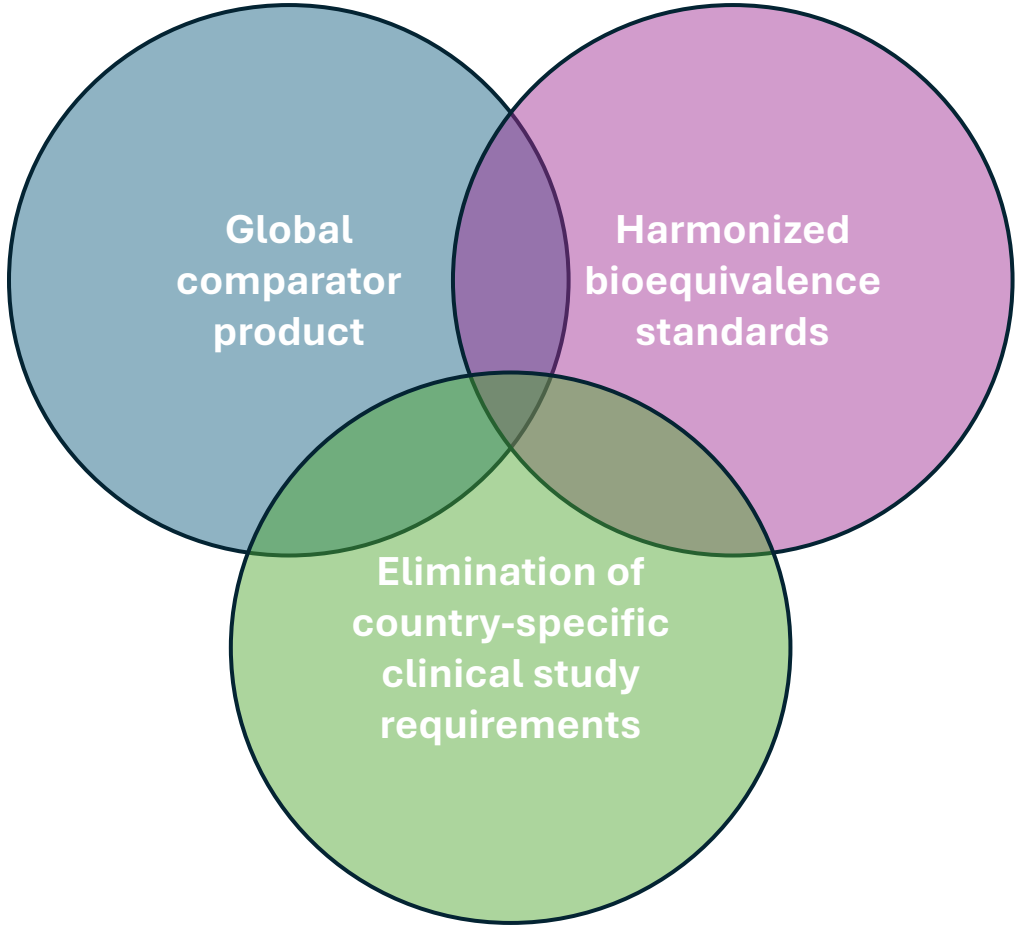
What do we mean by “Global Harmonization”?

Global harmonization means different things to different stakeholders:

For some, it focuses on streamlining clinical trials to avoid duplication in every new market.

For others, it’s about standardizing acceptable comparator products.

Others view it as aligning API, bioequivalence, and manufacturing standards across regions.



In this context, we will consider all of these aspects as integral to ‘global harmonization’ and examine their collective impact on patient access and regulatory efficiency.

Ongoing harmonization efforts

- International Council on Harmonization (ICH)
  - M9 (biowaivers) and M10 (bioanalytical method validation)
  - M13: Bioequivalence for Immediate-Release Solid Oral Dosage Forms
- World Health Organization
  - Prequalification of Medicines Programme
- International Pharmaceutical Regulators Programme (IPRP)
- Access Consortium
- International Coalition of Medicines Regulatory Authorities (ICMRA)
- The Generic Drug Cluster
- FDA/EMA Bilateral Parallel scientific advice (PSA) program

ICH Guidelines

ICMRA
International Coalition of Medicines Regulatory Authorities

IPRP
International Pharmaceutical Regulators Programme

ACCESS CONSORTIUM
AUSTRALIA
CANADA
SINGAPORE
SWITZERLAND
UNITED KINGDOM

World Health Organization

Main hypothesis: Single global development will improve patient access to generic and biosimilars medicines, improve patient outcomes and reduce health care costs

Methodology and approach

- Structured interviews with stakeholders (companies, experts, associations, regulators, etc.)
- Assessing pain points for developing generic and biosimilars medicines for global markets
- Collecting examples of products available in one market but not others

Scope and impact of the research project

Exploring how regulatory challenges impact market access for

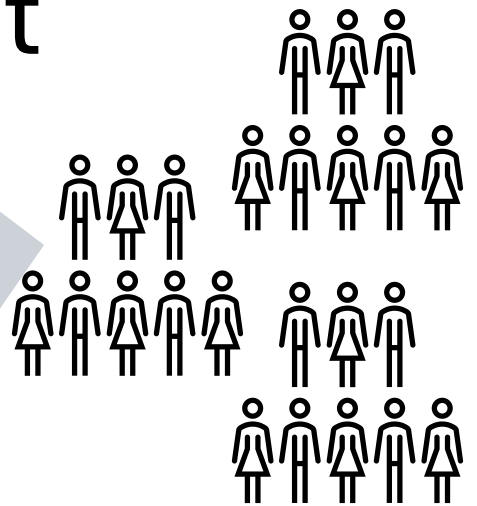
- **Simple Generics**
- **Complex Generics**
- **Biosimilars**
- **Orphan drugs**

Regulatory approval*

Drug enters the market

Providers can prescribe cheaper treatments

A larger number of patients will have access treatments



If the requirements to achieve this step were harmonized, entering more markets would maximize impact for patient access globally

Analyzing discrepancies in regulatory requirements across major geographies

- **US**
- **EU**
- **Canada**
- **Japan**

Reported themes and general pain points

Bioequivalence (BE) studies

- Multiple studies required for different markets
- Inconsistent study requirements across regulatory bodies
- Different acceptance criteria across regions resulting in
  - high costs and time investments
  - delays in market entry

Comparator product

- High cost of comparators for demonstrating equivalence
- Repeat testing required with locally sourced comparators (foreign comparators not accepted)
- Assumptions about equivalence not the same across regulatory bodies
- Difficulties in obtaining comparator products
- Unavailability of comparator products in certain markets

Clinical studies

- Varied requirements across markets for demonstrating equivalence, e.g.: Phase 3, modeling, alternative approaches, and RWE
- Local comparator product requirement discouraging market entry
- Population requirements:
  - Some markets require local population studies
  - Varying acceptance of foreign study populations

Active pharmaceutical ingredient -CMC

- Varied market (country) specific requirements i.e. purity levels, residual solvents
- Need for additional production/manufacturing processes, e.g.: higher purity level
- Differing interpretations of guidances, e.g.: ICH Q5E and ICH M9, i.e. use of surfactants

Complex product-specific challenges

- Complex products (e.g., inhalation, biosimilars) face varying requirements for approvals
- Device-related issues for combination products
- Formulation and manufacturing challenges
- Varying in vitro study requirements

Other regulatory themes

- Divergent impurity standards
- Immunogenicity requirements
- Packaging and presentation differences
- Stability testing
- Site inspections
- Move to low global warming propellants for inhalables

Regulatory divergence

- Differences between regulators (FDA, EMA, HealthCanada, PDMA) approaches
- Varying timelines for approvals across regions
- Inconsistent guidance for certain product types
- Different approaches to excipient evaluation
- Contradictory regulatory expectations

Other market access challenges

- Patent barriers and economic factors
- Reimbursement framework and policy differences
- Lack of innovator approval in certain geographies
- Local entity or manufacturing requirements in some markets
- Competition with local companies

Assessment of major categories of regulatory challenges encountered by companies

	Challenges	Generic/Biosimilar Company								
		1	2	3	4	5	6	7	8	9
1	Clinical Study Requirements	X	X	X	X	X	X	X	X	X
2	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	
3	Manufacturing and Production	X	X	X		X	X	X	X	X

Challenges with clinical study requirements

Challenge	Impact
Duplicate clinical assessment due to differing regulatory requirements	• Repeated testing for the same product in different jurisdictions • Varying requirements across jurisdictions for demonstrating bioequivalence (BE), e.g.: ▪ Clinical study requirements when in vitro BE is established ▪ Cross-over multi-dose in patient vs. cross-over single dose in healthy volunteers ▪ The need for Fasting/Fed Vs only Fasting or only Fed
Comparator product sourcing	• Difficulty sourcing comparator products in different jurisdictions • High cost of comparator products in certain jurisdictions • Challenge for generic entry when innovator is not approved in a market
Diverging patient population requirements	• Inconsistent inclusion/exclusion criteria, e.g.: ▪ The need to include patients from specific geographies ▪ Blue-eyed patients requirement for ophthalmic drugs

For biosimilars and some complex generic products large and costly end-point studies could be required for approval

Challenges with comparator product requirements

Comparator products are essential for proving bioequivalence, but their role in global development presents significant challenges.

The comparator product approved in each jurisdiction relies on the same pivotal studies.

Reference product access barriers:

- Region-specific reference product requirements
- REMS, Controlled substances, Orphan drugs
- Unavailability of comparator products in certain markets

Non-harmonized requirements:

- Regulators differ in acceptable comparator product sources

Duplicative Testing:

- Inability to reference the same comparator product across markets leads to repeated bioequivalence studies

Cost Implications:

- High costs associated with acquiring multiple comparator products (biosimilar and orphan) and conducting redundant studies

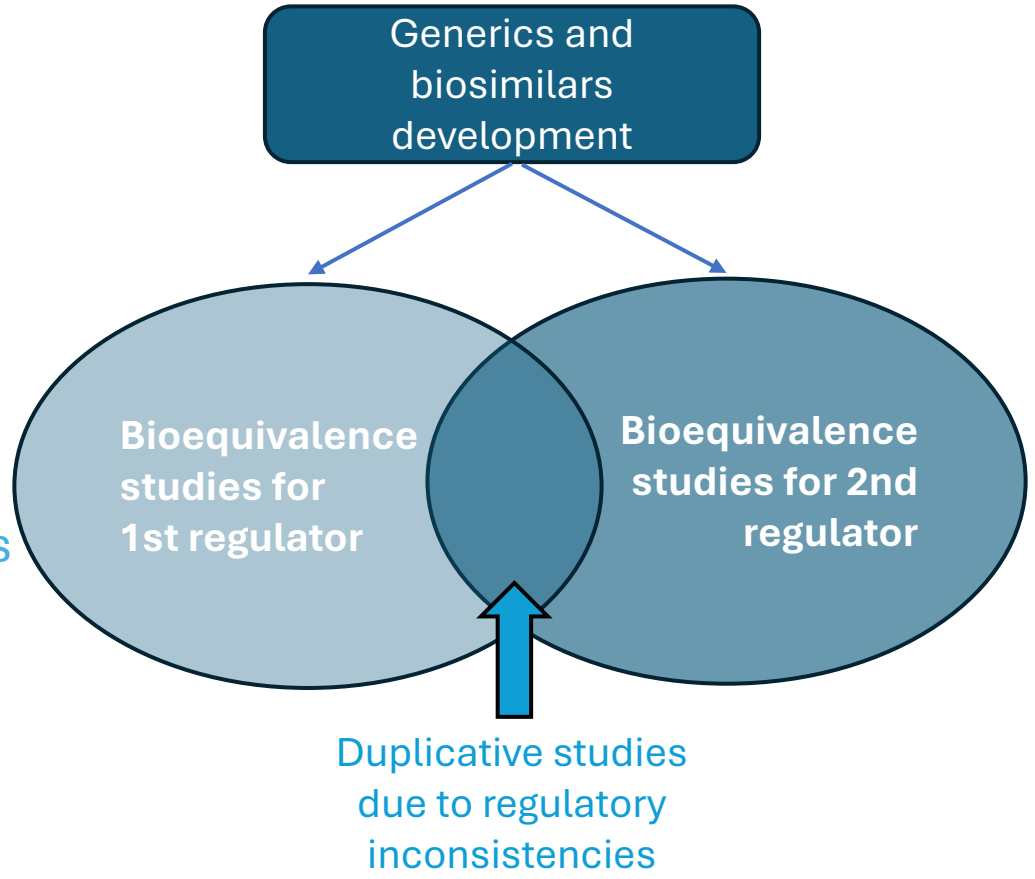


Diagram is just an illustration

Challenges in manufacturing and production

API purity issues

- Pain points: Diverging purity standards for APIs across different countries. Different residual solvents requirements; Different purity for peptides.
- **Impact**:
  - Need for region-specific manufacturing processes
  - Multiple supply chains with differing requirements
  - Delays market entry due to additional validation steps

Local entity or manufacturing requirements

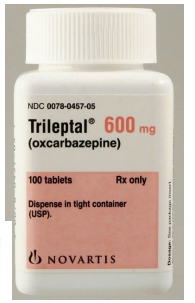
- Pain point: Some countries mandate local manufacturing of both the reference drug and the test drug for bioequivalence studies.
- Differences in manufacturing requirements between countries.
- **Impact:**
  - Adds complexity to production logistics and delay development timelines
  - Drives up costs for setting up local facilities or contracting local partners.

Other challenges

- Region specific device-related manufacturing challenges
- Facility inspections and compliance issues
- Difference in Pharmacopoeia and compendial requirements
- Stability-testing and packaging
- Batch size and post-approval requirements
- **Impact:**
  - Increased production costs
  - Need for additional characterization of drug-device combinations
  - Higher costs and delays in approval

Challenges with developing oral solid dosage products for multiple (global) markets

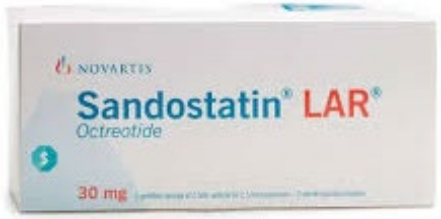
Need for separate BE studies with local comparator products even when comparator is the same across markets	Lack of availability of same BE strengths for comparator product across markets	Inconsistent BE study requirements for different markets such as Fasting/Fed Vs only Fasting or only Fed
Requirement for studies in local population which can be cost-prohibitive in certain markets (5-8X increase in cost)	Inconsistent acceptance criteria for BE study design, formulation differences, dissolution, etc. by regulators	Differing Pharmacopoeia and compendial requirements across markets
Different data requirements for highly variable drugs such as AUC vs Cmax by regulators	Varied and country specific BE, CMC requirements- packaging, stability (e.g. Zone II vs Zone IV), registration batch size	Request for Certificate of Pharmaceutical Product from specific jurisdictions, necessitating export from specific country which increases the cost considerably

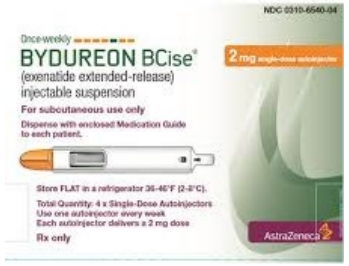


- ***Varying, redundant and market specific BE, CMC requirements, etc. create a huge barrier for market entry for small- and mid-size companies that cannot make the commercial business case especially when the market share is insufficient to sustain cost of development/investment.***
- ***Need for single global development especially for products with lower market share, low volumes***

Contradicting biowaiver requirements for additional proportional strengths for oral solid dosage forms could be prohibitive for development of these products from some markets

- Lack of alignment with approaches accepted by regulators across markets
  - Additional biostudies for non-biostrengths
  - Differences in use in dissolution study design: dissolution testing requirements for additional strengths, single unit testing requirement (Canada), difference in surfactant use in dissolution media (USA-yes, Canada – different level to establish sink conditions, EU – no surfactant).
- Canada requires extensive in vitro data to be generated, ~3X additional tests and time, upto $1M in cost for Canada-specific studies which could be prohibitive for a small market, missed opportunity cost for companies undertaking development of these products
- Additional BE studies required by EU as compared to US for proportional similarity across different strengths of same drug product ($1.5M cost vs $250K)





Complex regulatory challenges with divergent immunogenicity testing requirements would significantly impact generic peptide products

- Significant market approval timing disparities
- Varied immunogenicity study requirements- adaptive and innate studies
- Regional differences in testing and reporting thresholds (Inconsistent impurity control requirements- 0.10% in US vs 0.5% in EU and Canada)
- Regulatory guidance interpretation variations
- Regulatory uncertainty and changing requirements- impact on market authorizations of drugs already on the market
- Challenges with demonstrating device equivalence and Comparative Use Human Factors (CUHF) study requirements; Patent workaround complications
- Repeated characterization and market-specific development against identical reference product

Market specific regulatory requirements and increasing costs impacts development of inhalational products for multiple markets

- Divergence in PK study requirements for proportional dose- highest strength for Canada vs all strengths for US
- Varying acceptance of foreign comparator products, analytical requirements for BE studies
- Requirement for additional region-specific studies (such as PK study and lab work) to establish BE
- EU requires process validation prior to approval while US does not
- Varying acceptance level for alternate/in vitro approaches
- Uncertainty with shift to greener propellants
- Drug-device combination

- ***Regulatory divergences have particularly profound impacts on complex generics, where development costs are already substantially high***
- ***Significant gaps in development for certain markets due to company's inability to harmonize development programs across markets***

Biosimilar developers walk a tight rope with the ever-changing regulatory landscape

- Complex development requiring up to 300MM in investments and >6 years for global development
- High volumes and market prices make business cases stronger for highly regulated markets (US, EU, Japan), however high development costs (4-5X higher than semi-regulated markets) and complex IP make it less attractive for smaller/ emerging companies
- Requirement to use local comparator product to demonstrate CE and/or for CMC requirements- increases cost of comparator products in certain markets, unavailability of comparator product in certain markets
- Inclusion of local patient population in clinical studies by several regulators in LATAM, MENA and SEA
- Different formulations and presentations of products- strengths (25mg vs 50mg), self administered vs hospital administered, route of administration differences, etc.
- Human factor study requirements for drug-device combination products in the US and EU are complex and cost/time intensive, not required by LATAM, MENA and SEA
- Disparity in what regulators are looking for and their background understanding- scientific rationale vs rule book. Totality of evidence is fast becoming the norm to explain underlying differences (e.g., batch to batch variation impacting glycosylation, aggregation levels measured by different methodologies)

Advances in harmonization efforts in biosimilar development by US and EU regulators, such as acceptance of bridging studies for certain products have had significant impact on biosimilars development

Regulatory inconsistencies and technical classification decisions can have far-reaching implications for biosimilar development

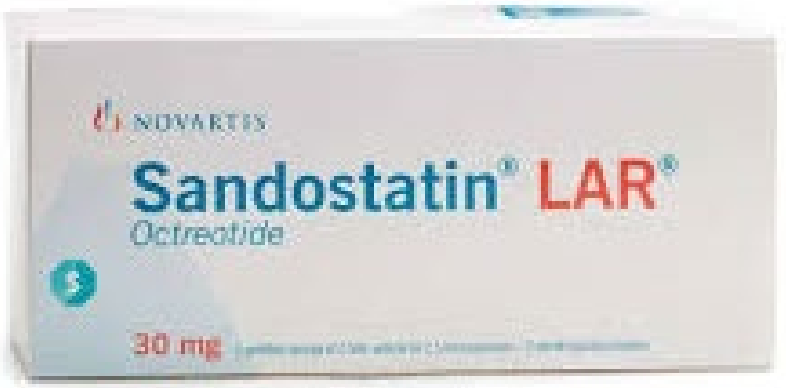
- Regulatory inconsistencies related to delivery devices not substantiated by scientific rationale, rigid requirements regarding similarity, despite identical active ingredients and demonstrated clinical performance create barriers to patient access
- Lack qualified resources and insufficient pharmacovigilance monitoring to assess the safety and efficacy of biosimilar interchangeability across jurisdictions
- Variations in classification of drug components (e.g.: hyaluronidase as an active substance vs excipient) across jurisdictions limits formulation development capabilities and development to cater to certain markets

Challenges with developing orphan drugs for multiple (global) markets

- Redundant testing requirements with local references/comparators
  - Comparator is often the same product in all jurisdictions and often manufactured in one plant for rare diseases
  - High cost of reference/comparator product
  - Difficulty with acquiring the reference product
  - Unavailability of multiple batches because it is an orphan drug
- Market-specific clinical study demands
  - Need to perform BE studies for each jurisdiction
  - Local patient population requirements
  - Limited number of eligible patients for orphan indications
  - Prohibitively expensive

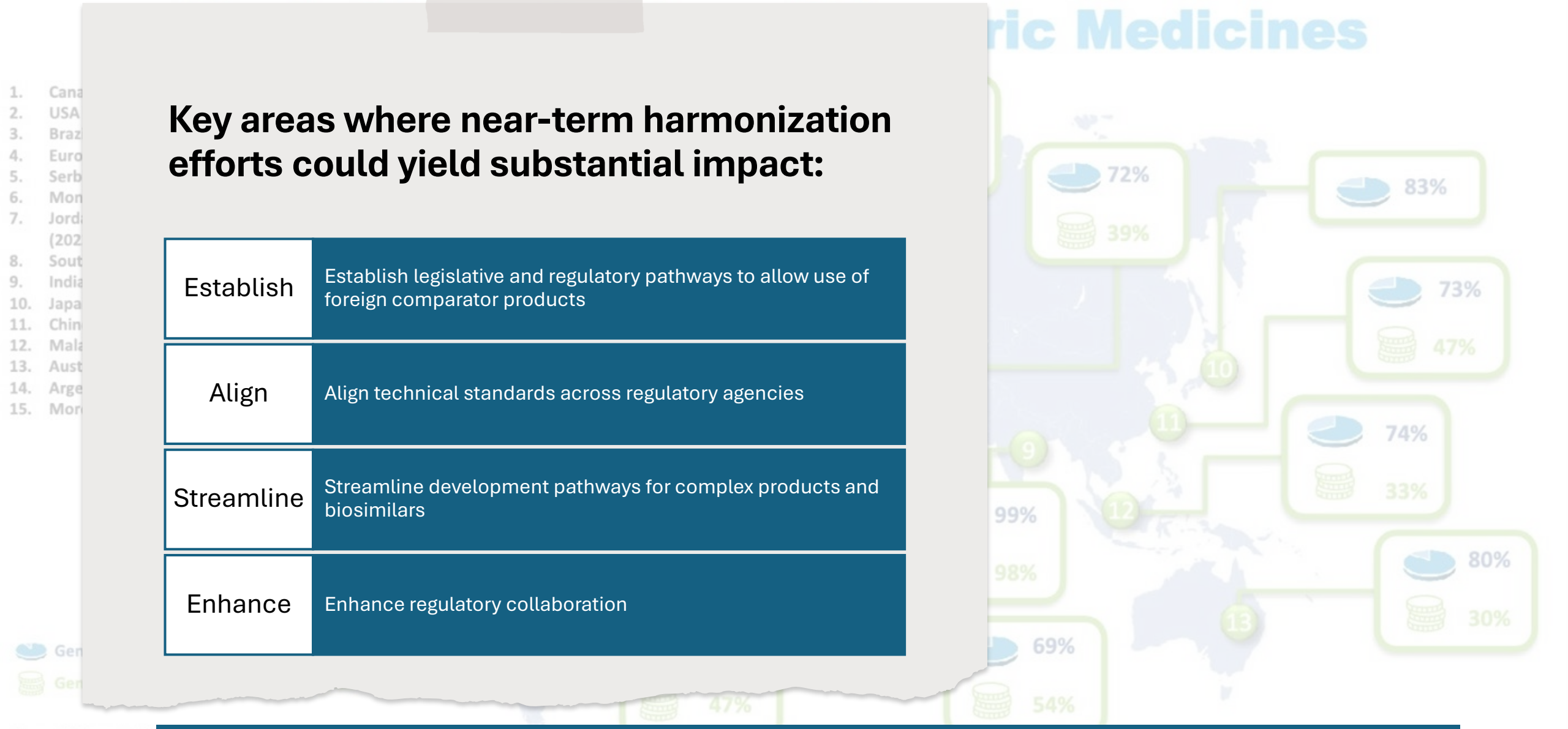
Lack of global harmonization makes development of orphan drugs less attractive for certain markets

- Inconsistent approaches to risk management plans across jurisdictions
- Risk Management Plan (REMS) additional requirements, additional delays (6-9 months) in acquiring comparator products due to obstacles from innovator companies including additional fee (20%-25%)
- In addition to high costs of reference products, companies also face burdensome market-specific study requirements
- Drop in drug price by 90% within 2 months of market entry making it hard for companies to mitigate cost of bringing drug to market
- Development becomes economically viable only in larger markets that can support the investment required, leaving smaller markets without access to more affordable options



Key areas where near-term harmonization efforts could yield substantial impact:

Establish	Establish legislative and regulatory pathways to allow use of foreign comparator products
Align	Align technical standards across regulatory agencies
Streamline	Streamline development pathways for complex products and biosimilars
Enhance	Enhance regulatory collaboration



“Can a single dossier support access to more patients in more markets?”

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