Original Article

Moving Towards a Single Global Approval of Drugs: From Concept to Reality

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Abstract

Access to high-quality pharmaceuticals is critical to achieving right to health. Despite advances in health-care technology, there are various hurdles to the availability of quality medicines in developing countries. Quality of medicines, and nationally regulated drug approval processes heavily influence drug prices. There are various obstacles to making high-quality medicines available worldwide. Efforts such as eCTD, the Drug Price Competition Act, USFDA's Generic Drug User Fee Amendment, emergency use authorizations, etc. are major endeavours aimed at simplifying and expediting the generic drug approval process. While these efforts are admirable, drug approval processes need to be harmonized to reduce costs, increase market competitiveness, and improve drug accessibility to the underprivileged. Significant differences between countries in application processes, prices, and study requirements, motivate pharma to focus on more profitable regions. Disparity in drug approvals also generate significant differences between developed and developing countries in quality and price of drug products. ICH reflection paper, in response to US FDA's recommendation for harmonizing generic drug approvals, is a significant step towards improving drug availability and access. At the same time, it is critical for the world to consider a single global system for drug approvals that can revolutionise the pharma industry by making even the most expensive drugs available to underprivileged regions.

Keywords: Drug approval; ICH guidelines; Generic drugs; Drug regulations; USFDA.

INTRODUCTION

In its constitution (1946), the World Health Organization (WHO) stated that "the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition (1). Ready access to quality medications is the sine qua non for implementing universal health. Despite widespread progress, many developing countries continue to lack access to affordable essential medications on account of barriers that prevent access to high-quality medications at a reasonable price, a violation of fundamental human rights (2).

Nonetheless, pharmaceutical quality standards are heavily influenced by a country's culture, lifestyle and economic situation, in addition to adaptation cost, market size, government regulations, affordability, culture, and many other factors. It is believed that having access to the world's safest and most advanced pharmaceuticals benefits Americans (2).

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The quality of medicines is important in addressing the global healthcare cost (3). Meanwhile, drug manufacturers and distributors have to seek approval from various regulatory agencies across multiple countries separately due to significant differences in procedures. Many countries formulate tedious, time-consuming regulatory hurdles (4), which increases pending applications and workload of regulatory authorities reviewing abbreviated drug applications. Rising application costs and stringent regulatory requirements are limiting the number of generic drug applications, thereby increasing drug prices. Simultaneously, the increasing number of applications delays the review and approval. A cost comparison for generics across the world is depicted in the figure 1. The Covid 19 pandemic brought to light the importance of expediting drug approvals, streamlining drug registration processes, and establishing global quality standards (5).

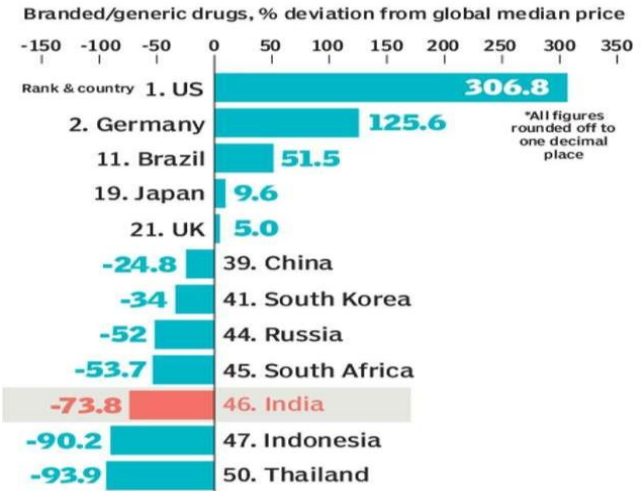

Figure 1: A cost analysis and comparison of medicines worldwide (2,7)

Cost of drugs plays a crucial role in public health

High cost of drugs is compromising patient compliance and health outcomes. One major reason for the rise in regulatory costs is the need to submit different application formats / data for generic approvals in different countries. When applying for marketing generics in multiple countries, the process becomes more complicated and the cost per application rises (6).

Cost-cutting forces manufacturers to compromise on material grades, flavors, and aesthetics, limits product approvals by selected countries and leaves consumers with fewer quality and pricing options. A common application process in multiple markets may accelerate the approval process and reduce the cost of generics drug development by harmonising scientific and technical standards worldwide (7).

Current drug approval scenario`

Global Generic and Biosimilar pharmaceuticals industry has made significant contributions to global health outcomes. In 2020 generics accounted for 60-80 percent of all medication sales volume ($390.57 billion in value) in major markets worldwide, with higher penetration in developed countries (6,8). A generic product may gain market access by demonstrating equivalence to a previously sold innovator product and submitting sufficient evidence to demonstrate safety and efficacy.

Individual law enforcement agencies have different regulatory definitions of generic drugs (9). For example, the United States Food and Drug Administration (US FDA or FDA) insists that dosage forms of a generic product must be identical to its reference standard (RS). On the other hand, EU, allows different dosage forms if bioequivalence is established. Furthermore, the FDA requires that the RS used in testing be a registered product in the United States, unlike Health Canada (8).

Despite simplifying biosimilar approval routes the cost of clinical trials remains high. Despite anticipated advances in regulatory science and characterisation capabilities, inventors and producers face significant risk. Emerging markets require a well-defined regulatory environment that allows for rapid product development in place of lengthy approval procedure without clear timeframes, a hazy understanding of clinical research design, requirements for additional resources, etc. Similarly, these obstacles also impede generic and biosimilar drug development. Regulatory delays are further amplified when companies strive to create a more inventive pipeline (6).

Room for Better Harmonization

Harmonization reduces the number of steps in document filing and develops standard elements to be submitted as part of the application, regardless of the region that grants approval (10).

Electronic common technical documents (eCTD)

The FDA accepts the Electronic Common Technical Document (eCTD) as a universal submission system because eCTD saves reviewers time by allowing them to search and edit the submission using computerised systems and reduces the burden and cost of the submission process.

Convergence in standards and regulations for eCTD review and approval can be further improved by developing guidelines for preparing a well-structured eCTD. Manufacturers or sponsors seeking marketing authorization can consider submitting the same eCTD application to multiple regulatory agencies around the world, allowing for simple and low-cost drug approvals (11).

Emergency use Authorization

The exigencies of the pandemic compelled USFDA to consider vaccines under Emergency Use Authorization, (EUA) characterized by conditional approval based on the results of two months of clinical trials. EUA differs from Biologic License Application, which requires six months of data and is approved in full. Companies seek EUA approval

through a 'rolling submission,' which expedites the process by allowing the FDA to review new data as and when submitted by the company (12).

Advancing Towards Global Approval for Generic Drugs

The FDA conducted a preliminary study of IQVIA MIDAS International Data after considering the possibility of expanding generic medicine availability and improving market competition beyond their existing markets. The study also included five EU countries (France, Germany, Greece, Poland, the United Kingdom, Japan, Canada, and Switzerland), as well as Australia and New Zealand. The FDA felt it was particularly important to investigate the possibility of nations gaining access to generic medications that are currently unavailable (13). FDA has brought about the following amendments and actions for the ease of registration of generics without compromising their quality standards.

1. FDA Drug Competition Action Plan – 2017

The US FDA does not have a direct role in drug pricing but is critical to regulating drug access. Consequently, FDA enacted the Drug Competition Action Plan (DCAP) in 2017 to endorse reasonable generic pricing while ensuring quality and ready access.

The FDA is attempting to remove barriers to generic drug development and market entry through DCAP to stimulate competition and make drugs more affordable. As a result, DCAP has partnered with the generic drug user fee programme II (GDUFA II) (14).

2. FDA- Generic Drug User Fee Amendment (GDUFA) II – 2017

GDUFA II aims to reduce the number of approval review cycles while increasing the number of approvals of safe, high-quality, low-cost generic drugs (15).

GDUFA II's objectives and commitments include the following:

✓ Facilitating development and review of abbreviated new drug applications (ANDAs) for complex generic products as shown in figure 2.

✓ New review objectives for priority ANDA submissions

✓ Increased transparency, monitoring, and fee relief (via a fee structure change) that benefits small businesses (15).

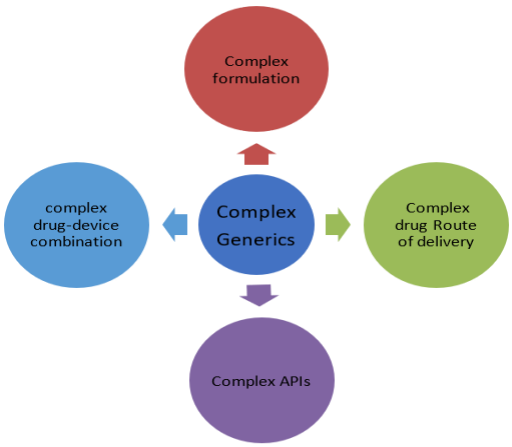

Figure 2: Complex Generics

The above strategy encourages competition and removes complexity and expedite generic drug approvals, while clamping down on direct to patient advertisements and prolonging prescription monopolies (see Figure 3) In 2019, GDUFA II, was re-launched with a few amendments including advanced standards for drug competition (15). Presently, GDUFA III amendments are ready for implementation in 2022.

Latest DCAP Updates

- Correspondence request to FDA: DCAP published a guidance in December 2020 that describes the process by which a generic drug development, generic manufacturer, or marketing company can apply to the FDA by providing all data related to a specific drug.

- Facilitating the discussion between FDA and ANDA applicants: A guidance issued in November 2020 facilitates discussions between the FDA and ANDA applicants for complex products, allowing the company to request meetings during product development, prior to submission, and during the review cycle, allowing for better communication and understanding of the needs.

- Identify References: This guidance explains how to isolate and recognise fee, reference standards, reference drugs, and the scientific basis for their application (16).

FDA's Proposal to ICH for global Harmonization of Generic Drug Standards

The FDA wants to bring uniformity in application information and technical standards for generic drugs around the world in order to simplify the drug approval process. By advancing international harmonisation standards for generic drug development, this may facilitate generic drug approval in multiple markets with a single set of globally valid data.

The International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is a global venue for pharmaceutical technical standards harmonisation, and the FDA proposal is a serious step that may benefit the entire global community. ICH can also create new guidelines for generic drug approval and review

processes in multiple regulatory regions using the same application data, even if the requirements in each country differ (17).

Benefits of better harmonization

Better drug approval process harmonisation may result in the following benefits:

- Increasing generic market competition would eventually bring competitive pricing, better availability and access to medicines.
- Generic drug approval across multiple markets would reflect the high standards and policies of FDA.
- Identifying and removing roadblocks would bring more generics into the market, increasing opportunities for manufacturers.

We believe that congruent generic approval standards would improve generic competition in the market. Lower prices, fewer shortages and access to better quality drugs would combine to improve the pharma market. While regulatory convergence would improve market competition and medical advancement, it would also eliminate barrier through collaboration with international regulatory partners. Collaboration between regulatory agencies would also help advance policies that assist pharma in product development (2).

ICH Reflection Papers on FDA's Proposal

The ICH Reflection Papers on February 6, 2019 discuss the need for harmonisation, its coverage, and its future, through recommendations for improving bioequivalence standards for complex generic drugs (3). and provides a rough outline of a "strategic strategy for designing and improving ICH Guidelines to promote the harmonisation of scientific and technological requirements for generic drugs." Endorsements are a component of the competition to improve the ICH guidelines. Among these will be the demonstration of equivalence for complex generic drugs (11).

In order to make progress toward harmonisation, the ICH proposed forming a Generic Drug Examination Committee to distribute tasks and recommend guidelines for better generic drug development (12). ICH believes that Harmonisation will increase market competition by increasing generic drug application, providing an impetus for developing drugs at a lower cost for greater outpatient access (18).

Establishment of Generic drug discussion group (GDG)

In 2019, the ICH established a generic drug discussion group (GDG) to collaborate with other international generics initiatives. The GDG was tasked with addressing issues concerning the harmonisation of scientific and technical standards for generic medicines and development/modification of guidelines for generics. GDG identifies areas for ICH harmonisation and evaluates the feasibility of harmonisation in various topics within existing regional regulatory frameworks (11).

Benefit-risk assessment, global drug development, and other highlights

By giving priority to public health, ICH guideline accepted an amendment on a well-structured common technical document namely ICH M4E (R2), describing a clinical overview to be included. Given the consequence of risk-benefit evaluation in drug regulation, the above amendment would encourage regulatory authorities in making decisions via more reliable data collected from clinical trials, as well as additional considerations such as the severity of disease and availability of other therapeutic options. These guidelines also include information about a public health point of view, to be executed by each ICH member country.

By unifying global drug approval of generics, the current ICH E17(General Principles for Planning and Design of Multi-Regional Clinical Trials) guidelines encourage strategies for multi-regional clinical trials data. The revised GCP guidelines (ICH E6) help to design the clinical trials, clinical trial management, clinical trial documentation, and reporting that can assure higher quality of drugs in the market worldwide(11).

Challenges in setting up a single drug approval globally

The following challenges need to be addressed for implementing single global approval of generic drugs to become a reality (8).

1.Clinical trials in different origins

Clinical trials should demonstrate that the generic drug product has the same efficacy as the branded product. Clinical trial reports provide evidence for safety and efficacy of the generic and facilitates its marketing (19).

Bioavailability and bioequivalence (BABE) studies are critical components of product development, but present an obstacle because BABE reports are likely to vary by region, ethnicity, genetic differences (20). In its guidance, issued on October 26, 2016, FDA mandates the recording of race and ethnicity data of subjects in clinical trials (21) Further, FDA mandates participation of subjects of multiple ethnicities as a key to achieve global health equity (22,23) Origin of diversity in clinical trials is depicted in Figure 3.

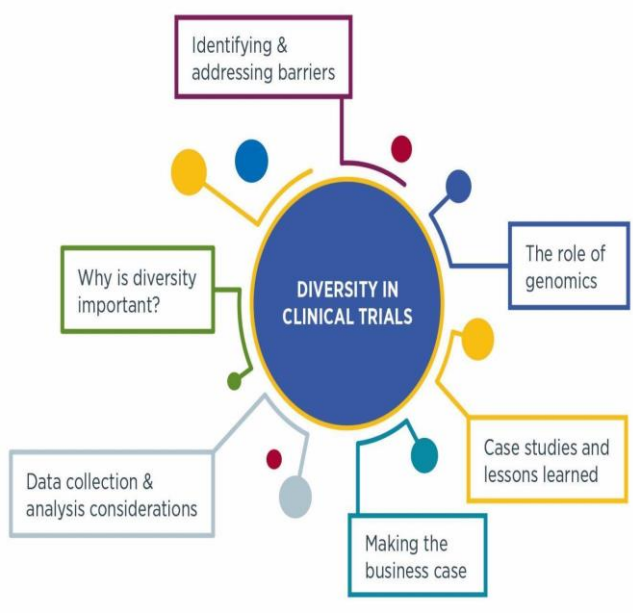

Figure 3: Diversity in clinical trials (18)

2. Willingness of the nations

Jurisdictions differ from country to country, as do their interests and requirements, (shown in table 1). SGAD may have an impact on standards, quality, clinical trials, and product costs depending on jurisdiction, economic status, quality expectations etc. Developed countries will be able to afford high-quality drug products at a premium price, whereas developing countries may be unable to allocate such large sums to the purchase of medicines.

Table 1: Comparative chart showing the regulatory requirements in USA, EU and India (32,33)

Requirements for Generic's Approval	US	Europe	India
Administrative Structure			
Regulatory Authority	Food and Drug Administration (FDA)	European Medical Evaluation Agency (EMEA)	**Central Government:** Central Drugs Standard Control Organization (CDSCO)
Registration	One type of registration	Four types of registration: 1. Centralized 2. Decentralized 3. Mutual Recognition 4. National	One type of registration
Application Type	Abbreviated New Drug Submission (ANDA)	Marketing Authorization Application (MAA)	MAA
Submission	eCTD	eCTD	CTD and Paper (Checklist)
Approval Timeline	18 Months	12 Months	~12 months
Pharmacopeia	US Pharmacopeia	British Pharmacopeia and European Pharmacopeia	Indian Pharmacopeia
Application	Form 356(h)	eAF Version 02	Form 44
Representative Agency	Required	Not- Required	Not- Required
Fee	$178,799	Different for different countries Application	$ 6,532.24
Required Documents			
Environment Assessment	Environment Assessment Statement (EAS) for categorical exclusion	Declaration for Environmental Risk Assessment is given with the Information from GMO or Non-GMO. The fresh/New	Environmental Risk Assessment if Given

	certificate in compliance with the law of EPA of US is provided	certificate if provided	
Patent/ exclusivity statement	Required	Required	Not- Mandatory
Certificate of suitability	Not Applicable	Required	Not Applicable
Letter of Authorization	Required	Required	Required
Quality of Product (QP) Certificate	Not required	Required	Not Required
Generic Drug Enforcement Act (GDEA) Certificate	Required	Not Required	Not Required
c-GLP/c-GMP Certificate	Required	Not Required	Required
Braille code	Not Required	Required	Not Required
Drug Composition Requirements			
IIG database (Inactive ingredient)	Must be within IIG Limit	No such database required	No such database required
Iron content	Maximum Daily Dose Should not be more than 5mg/ Day	No such database required	No such database required
Finished Product Control Requirements			
Batch size	A minimum 1,00,000 units	A minimum 1,00,000 units	A minimum 1,00,000 units
Packaging	A minimum of 1,00,000 units	No such requirements	No such requirements
No of batches	3	2	3
Assay	95 – 105 %	95 – 105 %	90 – 110%
Disintegration	This is not needed	Essential	Essential
Water contents	Required	Not Required	Required
Identification of Colour	Required	Not Required	Required
Fasting/fed state studies	Depends on product monograph	Fasting	Depends on product monograph
Retention of samples	For 5 Years	Not such requirements	3 years from the date of application submission
Post Approval Changes			
Guidelines	SUPAC (Scale up and Post Approval Changes)	Variations	Changes
Types	1. Minor change (CBE 0) 2. Moderate Changes (CBE 30) 3. Major Changes (prior Approval Changes)	1. Type IA Variations 2. Type IB Variations 3. Type II Variations	1. Major Changes 2. Minor Changes

3. Leadership Challenge:

which country will be willing to take leadership may be a dilemma while expecting FDA to initiate the same with the support of ICH and other interested parties.

4. Setting up a single body for approval

Regulatory agencies are divided by national boundaries, that frame individual regulations that safeguard patient's welfare and meet minimum quality requirements. Bringing different countries together to create a SGAD approval should be capable of finding unanimous unbiased solutions (24).

5. Managing Drug costs

High quality comes at a high cost. Mandating the highest possible standards require up to date technology, skilled manpower, and strong research support. Manufacturers catering to semi regulated markets may not comply with such requirement. High cost of medicines would compromise not only the healthcare sector but also the economy of developing economies. (25).

Strategies for managing risks:

Harmonisation of scientific and technical requirements for generics and generics benefits both domestic and international public health and health-care systems.

regional harmonization for regulatory requirements should amend ICH guidelines on scientific and technical standards for generic drugs to robust the regulatory pathways to achieve approval in multiple markets will be ideal. ICH should develop standard processes for drug approval in countries where harmonization is a shared concern (11).

Multinational generic supply chains were designed to suit multiple regulatory bodies. generic drugs are available to a greater degree developing countries as shown in the Figure 4.

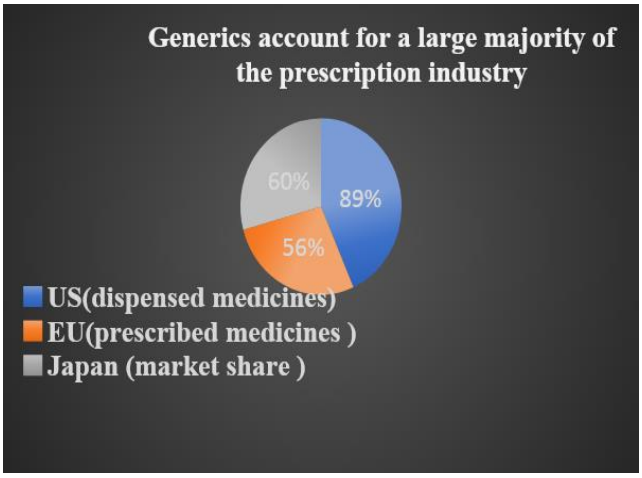

Figure 4: Market share of Generics in the prescription industry

Additional regulatory burden restricts marketing leading to shortages in select nations. Generic drug developer often ignores approvals because supplementary data generation is expensive. Robust harmonization facilitates generic manufacturers to submit a single application for universal marketing and will also increase the scope of generics, increase market size. Eventually, competition between multiple manufacturers would reduce the cost of medications. More applicants for generic approval would allow the industry to grow and increase consumer coverage across jurisdictions.

harmonization can modernize generic drug formulations and make them more cost-effective. for example, by reducing the number of bioequivalence studies required to meet requirements in multiple jurisdictions. When clinical trials studies are minimised, generics would reach the market faster and become more affordable. some bioequivalence studies require human participants, the delaying the release of drugs into the market. These contexts also limit the number of developers that enter the market, thereby prolonging patient access to better affordable drugs. Currently oncology generics (for rare conditions) fall under the above category.

Lastly, harmonization would improve the quality of generics by creating a globally acceptable culture of quality and encouraging compliance (26).

ICH Recommendations

a. ICH has revised BCS-based biowaivers (M9) and bioanalytical method validation (M10) guidelines and constructed guidelines for demonstrating equivalence. The new M9 guidelines recommend supporting the waiver of bioequivalence studies for highly soluble drugs belonging to BCS class I and class III (11,27). The M10 guidelines tries to harmonize the bioanalytical method validation during product development(28). Continuing attempts of harmonizing every part of drug product development may be essential for an effective harmonization of global regulations.

b. For non-complex generic dosage forms, ICH builds a series of guidelines for validating bioequivalence studies. ICH working group plans to consider the feasibility of harmonizing the bioequivalence testing across the markets and aligning them into a uniform guideline. These new guidelines will demonstrate equivalences that are to be submitted to the multiple regions for products of immediate-release oral dosage forms. ICH also aims to build a committee to validate these studies and narrow the therapeutic drugs and other variable drugs that need provide special consideration.

c. Series of guidelines contain the developed harmonization for oral and parenteral dosage forms and even strengthen the product line of bio-waivers. The nature of this bioequivalence analysis intends to allow for more than one reference drug to be used for bridging purposes. A three-way crossover analysis, for example, could allow generic drug details to be submitted for approval by using one test trial product in multiple regions (28).

d. ICH guidelines also focus on pharmaceutical equivalence and bioequivalence standards for complex API formulation, topical products, oral dosage forms and complex drug-device combinations. This harmonization may reduce the requirement of clinical bioequivalence studies (29).

Creation of a generic drug dialogue forum and connecting it to other international generics initiatives.

ICH established a discussion committee to further consider certain areas and opportunities for harmonized guidelines. The responsibility of these committees is to suggest for revisions that is required in a specific condition or for certain generic drug, by reviewing the existing guidelines(17).This committee must order the work areas carefully and they should communicate via mail, or by conducting an online meeting or by face-to-face meetings or by telecommunication.

Responsibilities of discussion committee are as follows:

- Amending the reflection paper Based on multi-regional input
- Advancement of generic standard harmonization by Identifying novel topics
- Examining current ICH recommendations as well as applicable WHO guidelines for generic drug requirements to find any missing area in generic drug guidance.
- Together with the ICH implementation subcommittee to determine regional ICH recommendations for generic drug implementation accuracy.
- To recommend the ICH management committee areas must Prioritize for harmonization
- The committee must discuss collaboration activities internationally. About current problems related to generic drugs.
- Publish international guidelines for bioequivalence studies for oral generic dosage form drugs.
- To assure that medicines which international buying agencies supply meets appropriate standards of safety, quality, and efficacy as prescribed by WHO.
- Avoid duplicating science that is already being discussed in other international forums.

The creation of this discussion committee would recognize the need for science and technological intervention as well as cooperation between experts to produce generic drug standards that are harmonized (30).

6. Future directions

The global generics market is growing as a low-cost alternative to branded products. The patent expiration of several drug products, an increase in the chronic disease burden, and federal incentives are all contributing factors. Robotic process automation (RPA) based on artificial intelligence (AI) is now used to design the eCTD, significantly speeding up the procedure. All of this will put significant strain on the government's regulatory agencies in the long run. All of this is likely to place a significant burden on regulatory agencies. According to Precedence Research, the global generic medicines industry will grow at a compound annual growth rate (CAGR) of 5.59 percent between 2021 and 2030, with a market value of $390.57 billion in 2020 and $574.63 billion in 2030 (31).

Countries should consider collaborating with ICH to develop harmonised, uniform requirements and processes for drug approvals, as well as a significant reduction in registration fees. Such a development could be a game changer in the generic drug market, eventually leading to the approval of new chemical entities.

Conclusion

The harmonisation of generic drugs offers significant public health benefits by streamlining, drug discovery across regulatory jurisdictions, and patient access to high-quality, low-cost pharmaceuticals. The registration of generics is a critical step forward in the advancement of health care, and it is critical for countries to support the harmonisation efforts undertaken by ICH expert working groups for the benefit of humanity.

Declarations

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