A Comparative Study of Regulatory Requirements for The Approval of Generic Drugs in The United States, European Union, And India

Ankita Suryawanshi[1], Avinash Mathapati[2], Nasheer Shaikh[3], Shruti Pandge[4], Aakansha Dhanasure[5], Pranita Nade[6], Vasudha Pargave[7], Pallavi Borphale[8], Asawari Dongre[9]
[1,2,3,4,5,6,7,8,9]*Department of Pharmaceutical Regulatory Affairs, Channabasweshawar pharmacy College (Degree), Latur413512. Maharashtra, India*

***Abstract*—Generic medications are crucial for lowering costs and increasing access to healthcare. Regulations ensuring, they are of the highest quality and have the same therapeutic effect as the original medications are necessary for their approval. With an emphasis on legal frameworks, bioequivalency research, data protection, patent limits, and approval processes, this article examines the regulatory requirements for generic pharmaceutical clearance in the US, EU, and India. A narrative examination was conducted using published scientific literature, government instructions, and regulatory papers. While the US employs the Hatch-Waxman Act's Abbreviated New Drug Application (ANDA) system, the EU uses the generic application process under Directive 2001/83/EC. The main legislation governing generic pharmaceuticals in India are the new pharmaceuticals and Clinical Trials Rules of 2019 and the Drugs and Cosmetics Act of 1940. A crucial prerequisite for proving that generic medications function similarly to their reference items is bioequivalence research.**

While the three regions differ in terms of patent protection, data exclusivity, regulatory processes, and study criteria, they share fundamental scientific concepts. The development and approval of generic drugs may be further impacted by recent events, such as the proposed modifications to EU pharmaceutical legislation and the reported 2026 update to India's bioequivalence study regulations. The evaluation emphasizes the necessity of improved regulatory harmonization, more precise norms, and increased collaboration amongst regulatory bodies, especially with regard to complicated generic medications. Better regulatory harmonization could save development costs, streamline applications across several markets, and facilitate the prompt supply of safe, efficient, and reasonably priced generic medications.

***Index Terms*—medication approval, bioequivalence, regulatory framework, ANDA, United States, European Union, India, and regulatory harmonization**

I. INTRODUCTION

Regulatory design played a major role in the creation of the modern generic drug business. The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417), often known as the Hatch-Waxman Act, created an accelerated approval procedure in the US along with patent-term restoration and exclusivity incentives for inventors [1,2]

Approximately 84% of US prescriptions were written using generics by 2015, yet less than 20% of drug costs were spent on them [1]. In exchange for demonstrating that its product is same and functions similarly in the body, a generic applicant may rely on safety and efficacy findings previously produced and funded by the original [2]. The mean generic-to-innovator geometric mean ratios for peak concentration and area under the curve were 1.00 (standard deviation 0.06) and 1.00 (0.04), respectively, in a review of 2,070 single-dose bioequivalence studies of generic products approved by the US Food and Drug Administration (FDA) between 1996 and 2007. It was discovered that in almost 98% of the studies, the generic area under the innovator by less than 10% [3].

The idea that bioequivalence regulations produce goods with nearly same exposure is supported by such data. However, they do not resolve all of the ongoing discussions in the literature on therapeutic equivalency and substitution [4]. The legal and administrative structures surrounding the underlying science are not revealed. There are regional differences in patent

linking, data protection periods, the definition of a reference product, the number of steps a dossier can go through, and the role of national versus central authorities. These distinctions are important for public health because they affect how quickly competition reaches patients, and they are important commercially because a generic developer aiming to target many markets must reconcile them. The issue is more acute for complicated generics, like drug-device combos and nanomedicines, where the definition of "the same" is debatable [5,6].

There are three benefits to comparing the US, EU, and Indian frameworks. The two most advanced debatable 50 generic regulatory systems and the primary benchmarks for international guidance are the United States and the European Union.India has a sizable domestic market and is a major provider of generics to other nations, thus both domestic and international supply are impacted by its regulations and all three have recently undergone or are undergoing change: India modified its bioequivalence permission regulations in 2026, and the EU is wrapping up the biggest overhaul of its pharmaceutical laws in twenty years. As a result, this evaluation marks each instrument's legal status and views the regulatory position as a shifting objective.

II. OBJECTIVE

1. To describe the nomenclature, application processes, and legal basis for generic medicine approval in the US, EU, and India.
2. To assess the requirements for bioequivalence evidence, biowaiver policies, intellectual property interfaces, and review procedures among the three jurisdictions.
3. To pinpoint areas of ongoing regulatory divergence and convergence, as well as the difficulties they pose for regulators and developers
4. To indicate the boundaries of the verified evidence and to differentiate adopted but pending actions and drafts from regulations and final guidance that are now in effect.

III. OVERVIEW OF GENERIC DRUGS

Definitions

Although the phrasing varies, each jurisdiction defines a generic by referring to an already-approved product. Article 10(2)(b) of Directive 2001/83/EC defines a generic medicinal product in the EU as one that has the same pharmaceutical form and qualitative and quantitative active ingredient composition as the reference medicinal product, and whose bioequivalency to that reference has been demonstrated by appropriate bioavailability studies [7].The US framework is represented by the content requirements for an ANDA, which include the rationale for submission, conditions of use, active ingredients, route of administration, dosage form, and strength [8].The idea is indirect in India. novel medications, investigational novel pharmaceuticals, bioequivalency and bioavailability studies, and ethics committees are all covered by the NDCT Rules, 2019 [9]. As covered in Section 8, a generic of a medication that is no longer a new medication is effectively governed outside of the new-drug permission procedure.

Bioequivalence as the scientific bridge

The rate and degree of absorption of a test product and a reference product are compared in bioequivalency investigations. The NDCT Rules, 2019 define a bioequivalency study as an investigation to ascertain whether the rate and degree of absorption of an active ingredient from a pharmaceutical formulation and the reference formulation, given in the same molar dose under comparable conditions, do not differ statistically significantly [9].

As discussed for the US and EU in Sections 6 and 7, regulators assess bioequivalency in practice by determining whether the confidence interval surrounding the test-to-reference ratio of exposure measures fits within predetermined bounds. A generic dossier often does not duplicate crucial clinical trials because the originator's safety and efficacy data are trusted [2,3].

Economic and public-health role

The US experience demonstrates that generics supply the vast majority of prescriptions for a small fraction of outlay, lowering costs and expanding access [1]. A pharmacokinetic comparison may not reflect equivalency of performance for complex goods, such as nanomedicines, locally acting products, and drug-device combos, so regulators have had to create product-specific strategies. An examination of the regulatory issues surrounding nanomedicines and their

derivatives raises the question of whether a "similar" or "generic" approach is more appropriate [5].and a recent evaluation of complicated generics in the US and EU recommends for more precise submission requirements, scientific guidance, and harmonized procedures [6]. The harmonization debate in Section 10 is framed by these considerations.

IV. UNITED STATES REGULATORY FRAMEWORK

Legal architecture

A patent-term extension for originators, a legislative exemption from infringement for activities required to seek permission, and an accelerated path for generic approval were all created by the Hatch-Waxman Act, which also changed food and drug law [2]. The ANDA pathway is implemented in accordance with section 505(j) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.94, which outlines the format and content of a 45-ANDA.In terms of content, the rule mandates, among other things, an application form, a table of contents, the foundation for submitting an ANDA, conditions of use, active components, administration route, dose form, and strength [8]. The ANDA Submissions: Content and Format, Revision 1 (June 2019) advice, which superseded the previous 2014 draft [10], provides the format and content guidance that the FDA is required to maintain [8]. The Common Technical Document format established by ICH is used to organize the dossier [11].

Evidence requirements

A product's bioequivalency to the reference listed medication must be demonstrated by an ANDA application [3]. Although generic chemistry, manufacturing, and controls are subject to the same regulatory oversight as innovator products, including adherence to current good manufacturing practices, safety and efficacy are not reestablished because they were documented in the originator's approval [3].Another need is labeling: 21 CFR 314.94(a)(8) calls for copies of the label and all labeling for the proposed product, and FDA guidance specifies when draft labeling can support approval and mandates that the label's content be submitted electronically [12]. The unique study-design regulations for immediate-release oral medications in the US and the EU are contrasted in Section 9.

Biowaivers

By using solubility, permeability, and dissolution data as a surrogate, the BCS-based biowaiver approach aims to lessen the necessity for in vivo bioequivalency studies [13]. Following approval by the ICH Assembly at Step 4 in November 2019, the FDA released the ICH M9 advice on biopharmaceutics classification system-based biowaivers in May 2021 [13]. Section 7.3 compares the US and EU's pre-M9 stances as well as the M9's actual reach.

Patents and exclusivity

The US system is unique in that it links the date of generic approval to patents. The "Orange Book," Approved Drug Products with Therapeutic Equivalency Evaluations, is published by the FDA and contains information on patents submitted by originators as well as reference listed drugs [2].

Every mentioned patent must be addressed by a generic applicant through a certification. 180 days of 12 exclusivity may be granted to the first applicant to submit a substantially complete ANDA with a Paragraph IV certification [2,14]. A Paragraph IV certification requires notice to the patent holder and inventor and declares that the patent is invalid or will not be infringed; if the patent holder files a lawsuit within 45 days, the approval may be stayed for up to 30 months.

Patents are used in conjunction with regulatory exclusivities. For five years after approval, the FDA cannot accept an ANDA for the same active moiety due to new chemical entity exclusivity; however, an ANDA with a Paragraph IV certification may be submitted four years later (the "NCE-1" date). If the case is filed inside the one-year window that opens four years after approval, the 30-month stay is extended to seven and a half years from the date of the originator's consent [14].

Certain modifications backed by fresh clinical research are subject to a three-year exclusivity [14]; 21 CFR 314.108 [14] describes these exclusivities. This architecture has encouraged strategic behavior in addition to producing very high generic penetration. Kesselheim and Darrow suggest revisions to the Act and discuss intentional exploitation of the Hatch-Waxman system as well as unforeseen events like the 2011 Supreme Court ruling in Pliva v. Mensing [1]. Comparatively speaking, a patent-linked system offers

chances to postpone entry through litigation and listing strategy, as well as powerful incentives to contest weak patents.

Review process and performance commitments

In the US, review dates are governed by the Generic Drug User Fee Amendments (GDUFA). The GDUFA III commitment letter, which covers the fiscal years 2023 to 2027, specifies, among other goals, that 90% of standard original ANDAs must be finished within 10 months of submission and priority original ANDAs must be finished within 8 months, subject to changes to the letter's goal dates [15].

Additionally, under GDUFA III, the FDA agreed to consider facility readiness when setting objective dates [15]. A comprehensive response letter sent on schedule nevertheless satisfies the aim because these objectives assess prompt regulatory action rather than approval. The program's continuation hinges on reauthorization, which was not confirmed for this study because GDUFA III only lasts until the end of fiscal year 2027.

Critical appraisal

With its published list of references and patents, performance objectives, and legislative content requirements, the US system provides certainty. Its reliance on the timing of litigation is a drawback. Because of patent certification and exclusivity, two applications with similar bioequivalency data can enter the market years apart [1,14]. This indicates that the scientific review is just one of multiple clocks controlling entry.

V. EUROPEAN UNION REGULATORY FRAMEWORK

Legal basis and data protection

Directive 2001/83/EC, the Community regulation on pharmaceutical products for human consumption, establishes EU law regarding generics [7]. Article 10(1) allows an applicant to exclude the findings of preclinical testing and clinical trials if they can demonstrate that the product is a generic of a reference medicinal product that has been approved for at least eight years in a Member State or in the Community. Ten years after the original permission of the reference product, a generic approved on this basis may not be released onto the market [7]. A reference medical product is defined as one that is approved under Article 6 based on a complete dossier under Article 8 [7]. For goods that do not strictly fit the criteria of a generic, such as due to a change in the route of administration or indication, Article 10(3) offers a different hybrid route, which typically requires additional documentation [7]. Directive 2004/27/EC increased the option of abridged applications and introduced the time structure presently known as "8+2+1." The initial ten-year period of protection may be extended to a maximum of eleven years if the holder of the marketing authorization obtains authorization for a new therapeutic indication of significant clinical benefit within the first eight years [16]. As a result, there are two separate clocks: one during which the originator's data cannot be referenced in a generic dossier, and another during which the marketing of an authorized generic is prohibited. This structure is going to change, as was covered in Section.

Procedures, dossier and the bioequivalence guideline

The EMA Guidelines for Bioequivalency Research (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) is the operational scientific guideline. It replaced the previous note for guidance and included suggestions on BCS-based biowaivers On January 20, 2010, the Committee for Medicinal Products for Human Use authorized it, and on August 1, 2010, it became operative [17]. in Appendix II, a typographical correction is indicated by the "Corr**" marker [17]. For immediate-release dosage forms having systemic action, the guideline lays out specifications for the planning, execution, and assessment of bioequivalency studies [17]. the key elements of the guideline are identified in a thorough discussion [18]. Directive 2001/83/EC serves as the legal basis for applications under Article 10(1) (generic), Article 10b (fixed combination), Article 10(3) (hybrid), and Article 8(3) (full).

It is applied across national, mutual recognition, decentralized, and centralized procedures [18].

The following are its primary technical points.

- The design: The typical design is a randomized, two-period, two-sequence, single-dose crossover; replicate designs are employed for highly variable items, while parallel designs are rare. The subjects should ideally be at least 18 years old and have a body mass index between 18.5 and 30 kg/m² [18].

- Research on feeding and fasting. Products are typically administered following an overnight fast. When a high-fat meal is recommended in the reference product's summary of product characteristics, a fed trial is necessary; tests conducted under both conditions are only necessary in rare circumstances [18].
- Two-phase designs. An altered significance level, such as a 94.12% confidence interval, is allowed for add-on designs [18].
- Analyzes and measurements. When the geometric mean ratio's 90% confidence interval is between 80.00 and 125.00%, bioequivalency is established [18].
- Analysis of variance with fixed effects is used to analyze the area under the curve to the last time point (or truncated at 72 hours) and peak concentration on the logarithmic scale. Almost always, the original molecule is utilized instead of a metabolite [18].
- Products that vary greatly. As long as the point estimate stays between 80.00 and 125.00%, acceptance limits for Cmax alone may be increased using a duplicate design in proportion to the reference's within-subject variability (where it surpasses 30%), up to a maximum of 69.84 to 143.19% [18].
- The therapeutic index of drugs is limited. Tightening the range to 90.00 to 111.11% might be required, however the guideline states that drugs cannot be classified based on a set of criteria; instead, this is decided on an individual basis [18].
- Content of the dossier. Except for pilot studies, where synopses are sufficient, all pertinent bioequivalency studies must be specified in Module 2.7.1 of the Common Technical Document and complete reports must be supplied [18].

Additionally, a 2012 opinion noted that different Member States may not follow the same regulations regarding substitution and switch ability. For instance, when determining whether generics might be exchanged, Denmark and Belgium interpreted bioequivalency data for narrow-therapeutic-index drugs differently [18]. This highlights a crucial point: replacement policy is still national, but the EMA guideline harmonizes the evidence required for authorization. A number of product-specific facts in that remark, such as how certain compounds are treated, are from 2012 and should be verified against the most recent EMA Q&A materials prior to use.

Biowaivers and ICH M9

On November 20, 2019, ICH Step 4 adopted the ICH M9 guideline on BCS-based biowaivers. It was approved by the CHMP on January 30, 2020, and it became operative in the EU on July 30, 2020 [19]. It eliminates products with a restricted therapeutic index, permits fixed-dose combinations where all active ingredients satisfy the requirements, and only applies to immediate-release solid oral dosage forms or suspensions intended to transport medication to the systemic The US position was reportedly limited to Class I prior to M9, whereas the EMA guideline allowed biowaivers for BCS Class I and Class III compounds [18].Both high-solubility classes are covered by the ICH text, with Class I having high permeability and Class III having low permeability [19].

The convergence of detail is also demonstrated in the technical text. While M9 categorizes the therapeutic material using the lowest observed solubility spanning pH 1.2 to 6.8 [19], the 2010 EMA guideline defined high solubility by reference to the dissolution of the maximum single dose in 250 mL over pH 1.0 to 6.8 [18]. These kinds of minor variations show why a single global standard is beneficial for developers: multiple submissions can be served by the same experiment.

The EU pharmaceutical reform: adopted by the Council, not yet in force

As of this writing, the biggest modification to the EU framework is not in effect The European Parliament and the Council reached a temporary agreement on December 11, 2025.Its fundamental components are an eight-year regulatory data protection period, a one-year market protection period (with extra periods allowed), and an eleven-year ceiling on the total regulatory protection time [20,21]A transferable data exclusivity voucher that offers an additional 12 months of data protection for one authorized product is created for priority antimicrobials [20].The new standard protection is nine years (eight plus one), with two additional one-year market-protection extensions available, a prohibition on patent linkage, and a clause stating that market protection does not apply in a

Member State if the authorization holder fails within three years to meet a request to supply sufficient quantities, according to a law firm summary of the provisional text published on March 6, 2026 [23]. According to the Council, submitting proposals for procurement bids will fall under the Bolar exemption [22]. The pharma package was approved by the Council on September 28, 2026. According to the Council itself, the regulation and directive will come into effect following publication in the Official Journal and must now be approved by the European Parliament [22]. According to the sources, the reform should be categorized as having been approved by the Council but not yet being implemented.

Directive 2001/83/EC as outlined in Section 7.1 is still in effect until it is published. This status may have changed, so authors should check the Official Journal and the Parliament's plenary record right before submitting. The reform has two major implications for generics. The maximum remains at eleven years, which is also the present maximum under the 8+2+1 formula, but the baseline protection prior to generic market entry drops from ten years (8+2) to nine (8+1) [16,23]. Additionally, it specifically eliminates patent linking, which is the US system's most distinctive feature (Section 6.4) [23].

The United Kingdom

The UK has its own system since Brexit. Generic applications are governed by Regulations 51 (Northern Ireland) and 51B (UK) of the Human Medicines Regulations 2012, which are comparable to the former Article 10(1) of Directive 2001/83/EC; Regulations 52 and 53 address hybrid and biosimilar paths [24].

According to MHRA guidance on comparator products, reference medicinal products must adhere to regulation 48(2), comparator products used in bioequivalency studies should be representative of the UK reference product, and the guidance applies to UK-wide applications submitted on or after January 1, 2025, in accordance with the Windsor Framework arrangements [25].Therefore, even though its legal lexicon is still similar to that of the EU, the UK is a unique country with its own reference-product rationale for a multi-regional developer.

Critical appraisal

When a generic can file (data protection), when it can be sold (market protection), and how bioequivalency is demonstrated (guideline) are three questions that the EU model divides but the US system combines. The revision affirms that it does not associate approval with patent status [23]. The cost of this division is that substitute, pricing, and reimbursement differ by Member State, and patent issues are settled nationally, outside of the regulatory procedure [18].

VI. INDIAN REGULATORY FRAMEWORK

Institutions and legal basis

The Drugs and Cosmetics Act of 1940 and Drugs in India are governed by its rules. The NDCT Rules, 2019 (G.S.R. 227(E), 19 March 2019), which were established under sections 12 and 33 of the Act and apply to new drugs, investigational new drugs for human use, clinical trials, bioequivalency and bioavailability studies, and ethics committees, designate the Drugs Controller (India) as the Central Licensing Authority [9]. State Licensing Authorities are defined by the Drugs and Cosmetics Rules, 1945 [9], which set them apart from this central authority. the current consolidated text is published by CDSCO; the version retrieved for this review states that it has been amended up to G.S.R. 21(E) of 18 January 2022 [9]. Additional amendments, such as those on standalone bioanalytical laboratories (G.S.R. 605(E), 31 August 2021), deemed approvals (G.S.R. 778(E), 14 October 2022), and registration of contract research organizations (G.S.R. 364(E), 11 May 2023) [26]

The “new drug” concept and the position of generics

In contrast to the EU's Article 10(2)(b), the Indian framework does not define a generic. Rather, it categorizes medications as either new or not. Rule 2(w) defines a "new drug" as a medication that is not commonly used in the country and has not been approved as safe and effective for its claims; a medication that has been approved for some claims but is being proposed for modified or new claims; certain fixed-dose combinations; modified-release forms and novel delivery systems; and vaccines and biological products [9].Pharmaceuticals stay novel for four years following approval from the Central Licensing Authority, according to an explanation, with the exception of modified-release and biological

categories [9]. It is erroneous to compare this four-year rule to data exclusivity in other jurisdictions. It is a categorization rule rather than a temporary permission to stop others from using data. Subsequent iterations of a previously approved medication stay in the new-drug pathway until the term expires because, on a literal interpretation, the explanation relates to the medication rather than a specific application. the sources that were retrieved and included in the verification checklist did not look at the specific application requirements for such follow-on items or the procedure by which a product that is no longer considered novel is licensed by State Licensing Authorities under the 1945 Rules. Additionally, no statutory data-exclusivity term or patent-linkage mechanism comparable to those in the US and EU was found in the instruments examined by the review; the lack of evidence should not be interpreted as proof of absence, and the authors could address this using primary Indian sources.

The 2026 amendment for export-oriented studies

The New Drugs and Clinical Trials (Second Amendment) Rules, 2026 were announced as G.S.R. 50(E) on January 21, 2026, and went into effect ninety days after they were published in the Official Gazette, according to a law firm study dated January 30, 2026 [27]. The amendment establishes a narrow exemption from prior authorization for specific oral dosage form bioequivalency studies carried only solely for export. Such research may start with a prior notification in Form CT-05 and an acknowledgment from the Central Licensing Authority in the absence of a Form CT-07 authorization. The specified requirements include a single-dose, two-period, two-sequence, two-treatment study involving healthy adult volunteers, approval by a registered ethics committee, a medication already approved in India or at least one of the United States, European Union, Japan, Australia, Canada, or the United Kingdom, and a minimum of eighteen subjects. Hormones, pharmaceuticals with a narrow therapeutic index, narcotic or psychotropic compounds, highly variable commodities, and cytotoxic medications are all considered exempt [27]. According to the same source, the authority handles between 4,000 and 4,500 bioequivalency applications annually [27]. The precise wording, start date, and any subsequent corrigenda must be verified from the Gazette notification before to publishing because this is secondary commentary. The amendment is important from an analytical standpoint for two reasons. It extends a logic that already exists where the Rules offer speedier handling of pharmaceuticals licensed in specific countries [9,27] by moving a high-volume, low-risk category of study from authorization to notification and making reliance on reference jurisdictions clear.

VII. COMPARATIVE ANALYSIS

The three approaches provide structurally distinct answers to the same topic, which is how much a generic application must demonstrate and when it may enter. They are compared on the dimensions discussed above in Table 1. Rather than indicating that a requirement is absent, cells labeled "not verified" highlight gaps in the review's evidence basis.

Table 1. Comparing the frameworks for approving generic drugs

Dimension	United States	European Union	India
Core legal basis	FD&C Act section 505(j) and 21 CFR 314.94 [2,8]	Directive 2001/83/EC, Article 10 [7]	NDCT Rules, 2019 under the Drugs and Cosmetics Act, 1940; pathway for drugs no longer “new” not verified [9]
Main authority	FDA	National authorities, EMA and the Commission through national, mutual recognition, decentralized and centralized procedures [18]	CDSCO as Central Licensing Authority, with State Licensing Authorities [9]

Reference product	Reference listed drug identified in the Orange Book [2]	Reference medicinal product authorized under Articles 6 and 8 [7]	Reference formulation named in the bioequivalence definition; no orange Book equivalent identified [9]
Evidence beyond bioequivalence	Chemistry, manufacturing and controls oversight as for innovators; labelling copies [3,8,12]	Common Technical Document; list of all bioequivalence studies in Module 2.7.1 [18]	Fourth Schedule documents, ethics-committee approval, registered study centre [9]
Bioequivalence criterion	90% confidence interval of the parent compound as usually recommended (2012 description) [18]	90% confidence interval within 80.00 to 125.00% for area under the curve and Cmax, with defined exceptions [18]	Defined in the Rules as absence of a statistically significant difference [9]; operative acceptance limits in CDSCO guidance, not verified
Biowaivers	ICH M9 final guidance, May 2021 [13]	ICH M9 in effect from 30 July 2020 [19]	Not verified
Regulatory data protection	5-year new chemical entity exclusivity (4 years to file with a Paragraph IV certification); 3-year exclusivity for certain changes [14]	Currently 8+2+1 years [7,16]; 8+1 with conditional extensions, capped at 11 years, under the pending reform [20,22,23]	No equivalent identified; “new drug” status lasts four years from permission [9]
Patent interface	Orange Book listing, certification, 30-month stay, 180-day exclusivity [2,14]	No linkage in approval; the reform bans patent linkage [23]	Not verified
Review-time commitments	GDUFA III: 90% of standard original ANDAs acted on within 10 months, priority within 8 months [15]	Not verified in this review	Decision within 90 working days on bioequivalence study permission, with deemed approval [9]
Latest change	GDUFA III in force for fiscal years 2023–2027 [15]	Council adoption of the pharma package on 28 September 2026 [22]	NDCT Second Amendment Rules, 2026 (G.S.R. 50(E)), reported [27]

Register of status divides instruments according to their legal standing.

As necessary for a fair reading of Table 1, Table 2

Table 2. The main instruments' current state

Instrument	Status	Basic for classification	Ref.
21 CFR 314.94	In force (regulation)	eCFR page current at retrieval	[8]
FDA ANDA Submissions: Content and Format, Rev. 1 (June 2019)	Final guidance, non-binding	Final guidance document; earlier 2014 version was a draft	[10]
GDUFA III commitment letter	In effect, fiscal years 2023–2027	FDA commitment letter	[15]
FDA ICH M9 guidance (May 2021)	Final guidance, non-binding	FDA guidance document	[13]
Directive 2001/83/EC and 2004/27/EC	In force (EU law) until replaced	EUR-Lex texts	[7,16]
EMA Guideline on the Investigation of Bioequivalence, Rev. 1/Corr**	Final scientific guideline, effective 1 August 2010	EMA document history	[17]
ICH M9 (EU implementation)	Final, effective 30 July 2020	EMA document history	[19]

EU pharma package (directive and regulation)	Adopted by the Council 28 September 2026; Parliament approval and Official Journal publication pending; not in force	Council press release	[22]
NDCT Rules, 2019 (consolidated to G.S.R. 21(E), 2022, and later amendments)	In force	CDSCO text and notification list	[9,26]
NDCT Second Amendment Rules, 2026	Notified; effective ninety days after Gazette publication (secondary source)	Law-firm analysis; Gazette text to be confirmed	[27]
MHRA application and comparator guidance	Current guidance	GOV.UK pages	[24,25]

What the comparison shows

First, each system runs on a different set of clocks. Review time and entry time can differ significantly in the US since entry is controlled by a mix of exclusivity periods and patent litigation [1,14]. Data protection and market protection, which are separate from patents, are the governing clocks in the EU [7,16]. Rather than determining who may depend on whose data, the four-year new-drug period in India determines which regulatory process is applicable [9]. Practitioner summaries frequently treat them as counterparts, which obscures the true distinctions between the purposes of each rule.

Second, the scientific core is the most convergent element but not fully so. Both US and EU frameworks Bioequivalency studies, a 90% confidence interval, and 80 to 125% limitations for common products are the foundation of both US and EU frameworks [18]. According to a 2012 comparison, the FDA generally recommended both fasting and fed studies for immediate-release products, while the EMA typically only required fed studies in exceptional cases. Additionally, the two agencies handled highly variable drugs differently: the FDA allowed scaling for Cmax and area under the curve and used a different regulatory standard deviation, while the EMA only permitted widening for Cmax [18].

Before being reiterated as current law, these 2012 findings must be compared to the most recent FDA product-specific guidelines and EMA Q&A papers. Because it replaced regional viewpoints that had diverged on Class I and Class III chemicals, ICH M9 indicates true convergence on biowaivers [18,19].

Third, India's rules are more explicit about the conduct and protection of the study than about the generic dossier The 2026 amendment illustrates a regulator shifting to notice for low-risk export research [27]. The Rules provide detailed information on ethics committee makeup, center registration, record preservation, and compensation [9]. While the Rules define bioequivalency as the lack of a statistically significant difference [9], contemporary practice in the US and EU uses equivalency criteria based on confidence intervals [18]. The operative acceptance criteria are likely to be found in CDSCO guidelines, so these are not necessarily in conflict. However, the issue should be settled from CDSCO guidelines before the paper specifies how Indian studies are evaluated.

Fourth, the pending EU reform narrows one of the largest structural differences. While the reform's conditional extensions linked to supply responsibilities introduce a public-health condition that has no direct counterpart in the US or Indian documents analyzed [23], its prohibition on patent linkage further highlights the difference with the US.

VIII. CHALLENGES AND REGULATORY HARMONIZATION

Scientific divergence

While acknowledging that harmonization was not a goal of the 2010 EMA revision, a 2012 analysis found that the major agencies demonstrated a fair degree of consistency but still disagreed on highly variable drugs, narrow-therapeutic-index drugs, the use of metabolite data, and conditions for biowaivers. It concluded that global harmonization should be the

next step [18]. A portion of this agenda for biowaivers was handled by ICH M9 [19]. The authors should update this part with the most recent EMA and FDA positions, as the remainder is dependent on current guidance that this analysis did not completely extract.

Intellectual-property interfaces

A system that favors patent challenges can also be deliberately employed, as demonstrated by the US experience. Kesselheim and Darrow demand that the Act be updated, citing both intentional manipulation of the Hatch-Waxman process and unforeseen consequences of court rulings [1].

By outlawing patent linking and expanding the Bolar exemption to cover procurement tender applications, the EU is taking a different approach [22,23]. These decisions represent varying opinions regarding the appropriate venue for resolving patent disputes. Each alternative trades entry speed against legal certainty for both parties, therefore there is no unbiased comparison.

Complex generics

The question of whether a follow-on is a generic or a "similar" product has immediate regulatory implications for nanomedicines and other complicated products [5]. Agencies must harmonize frameworks, offer scientific guidance, and specify submission procedures for such goods, according to a 2024 assessment of complex generics in the US and EU [6]. Divergence is most likely to persist in reference goods and distributed marketplaces because product-specific data is more challenging to standardize than pharmacokinetic equivalency.

Multi-market development requires a reference product that has been approved by regional regulators. UK standards describe how non-UK comparator products may be used in bioequivalency studies and require comparators to be representative of the UK reference product [25] Authorization harmonization does not provide substitute harmonization, as seen by variations in switchability decisions for narrow-therapeutic-index medicines among EU Member States [18].

For export-oriented studies, India's 2026 amendment requires prior permission in designated reference jurisdictions [27], a type of regulatory dependency that other systems may examine.

Capacity and predictability

Only when the system is capable of fulfilling performance commitments are they meaningful. According to reports, the Indian authority processes 4,000 to 4,500 bioequivalency petitions annually [27], and GDUFA III integrates facility preparedness into objective dates [15]. Applicants' predictability is influenced by both the regulations' wording and operational variables.

Routes to further harmonization

These three mechanisms, which are presented here as the reviewers' interpretation rather than the results of the referenced sources, seem to be the most promising. First, as M9 accomplished for biowaivers, ICH should continue to be used to transform regional bioequivalency practices into common guidelines [19]. The second is structural reliance, in which bioequivalency research carried out in accordance with a reference authority's requirements is accepted by a regulator, as India has started to do for export studies [27]. The third is that coordinated product-specific guidance for complex generics is lacking in the literature [5,6].

IX. FUTURE PERSPECTIVES

Over the coming years, a number of factors will influence the comparison. The crucial issue in the EU is implementation: the new protection durations, supply requirements, patent-linkage ban, and Bolar restrictions will require transposition and useful guidance after the Parliament completes its approval and the texts are published [22,23]. The architecture of the upcoming user-fee period will determine whether review performance goals and the handling of complicated generics alter in the US, as GDUFA III encompasses fiscal years 2023 to 2027 [15]. This assessment did not confirm the current state of that procedure. After data accumulates, the practical impact of the 2026 amendment on study volumes and review periods in India can be evaluated [27]. Outside readers might benefit from a more precise explanation of the approach for generics that are no longer novel medications.

Three deficiencies are apparent to the research community: comparative assessments of how agencies handle complicated generics; analyzes of how Indian bioequivalency permission deadlines function in

practice; and empirical investigations comparing time to first generic entry across the three systems [5,6].
In order to lessen the reliance on secondary summaries that this review has had to use for the most recent changes, authorities should also publish consolidated, version-dated texts of guidance and rules.

X. DISCUSSION

Comparing the regulatory systems for generic drugs in the US, EU, and India reveals significant regulatory distinctions as well as shared scientific principles. Bioequivalency is a crucial part of approval, and all three areas strive to guaranty the therapeutic equivalency, safety, and quality of generic medications. However, variations in regulatory processes, data exclusivity, patent protection, and approval processes may affect development costs and time to market. Although it relates generic entry to patent certifications and exclusivity terms, the US system offers a structured ANDA mechanism. Although national variations in substitute policies persist, the EU offers harmonized bioequivalency principles and separates patent-related concerns from regulatory data protection. Further clarity of the clearance process for well-known generic medications would enhance regulatory transparency in India, where the regulatory structure is concentrated on new drug permits and bioequivalency research criteria. International harmonization using ICH rules can expedite applications across various markets and minimize duplication of studies, especially for bioequivalency and biowaivers. However, product-specific data beyond traditional bioequivalency studies may be needed for complicated generics. Therefore, in order to facilitate prompt access to reasonably priced, safe, and effective generic medications, increased regulatory collaboration, updated guidelines, and transparent implementation of regulatory changes are crucial.

XI. CONCLUSION

The availability of safe, efficient, and reasonably priced healthcare is greatly enhanced by generic medications. To guaranty the quality and therapeutic equivalency of generic medications, regulatory frameworks have been established by the US, EU, and India. Their approval processes, bioequivalency standards, patent protection, and data exclusivity clauses, however, are different. To regulate generic-related development, the US utilizes the ANDA pathway, the EU uses the generic application procedure, and India employs the New Drugs and Clinical Trials Rules of 2019 and the Drugs and Cosmetics Act of 1940.Pharmaceutical producers continue to face difficulties due to variations in regulatory standards and implementation, despite the fact that bioequivalency is the basis for generic medicine approval in all three regions. Initiatives for international harmonization, like as ICH guidelines, can lessen these disparities and streamline the approval procedure. More regulatory cooperation, more explicit regulations, and improved approaches for complex generics are needed to reduce development costs and expedite market entry things considered, harmonizing regulatory requirements while upholding strict quality, safety, and efficacy standards can boost the generic drug market and encourage more access to reasonably priced medical care globally.

REFERENCES

[1] S. Kesselheim and J. J. Darrow, “Hatch-Waxman turns 30: Do we need a re-designed approach for the modern era?” *Yale Journal of Health Policy, Law, and Ethics*, vol. 15, no. 2, pp. 293–347, 2015. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/26333236/

[2] Congressional Research Service, The Hatch-Waxman Act: Over a Quarter Century Later, CRS Report R41114. Washington, DC, USA: Congressional Research Service, Dec. 5, 2012. [Online]. Available: https://www.everycrsreport.com/files/20121205_R41114_5b676e75fcbb7c24c109c92b96f13e64394fa412.html

[3] B. M. Davit et al., “Comparing generic and innovator drugs: A review of 12 years of bioequivalence data from the United States Food and Drug Administration,” Annals of Pharmacotherapy, vol. 43, no. 10, pp. 1583–1597, 2009, doi: 10.1345/aph.1M141.

[4] R. K. Verbeeck, “Bioequivalence, therapeutic equivalence and generic drugs,” Acta Clinica Belgica, vol. 64, no. 5, pp. 379–383, 2009, doi: 10.1179/acb.2009.063.

[5] S. Mühlebach, "Regulatory challenges of nanomedicines and their follow-on versions: A generic or similar approach?" Advanced Drug Delivery Reviews, vol. 131, pp. 122–131, 2018, doi: 10.1016/j.addr.2018.06.024.

[6] S. Patil, S. Kumar, D. M. Rao, and K. Rewatkar, "Current regulatory framework and challenges for the approval of complex generics in the US and the EU," Current Indian Science, vol. 2, 2024. [Online]. Available: https://www.eurekaselect.com/article/136589

[7] European Parliament and Council of the European Union, "Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use," 2001. [Online]. Available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32001L0083

[8] United States Government, "21 CFR 314.94: Content and format of an ANDA," Electronic Code of Federal Regulations. [Online]. Available: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-314/subpart-C/section-314.94

[9] U.S. Food and Drug Administration, ANDA Submissions—Content and Format: Guidance for Industry, Rev. 1. Silver Spring, MD, USA: FDA, Jun. 2019. [Online]. Available: https://fda.gov/media/128127/download

[10] N. Rafi, D. S. Sandeep, and V. Anoop Narayanan, "Regulatory requirements and registration procedure for generic drugs in USA," Indian Journal of Pharmaceutical Education and Research, vol. 52, no. 4, pp. 544–549, 2018, doi: 10.5530/ijper.52.4.63.

[11] U.S. Food and Drug Administration, Acceptability of Draft Labeling to Support Abbreviated New Drug Application Approval: Guidance for Industry. Silver Spring, MD, USA: FDA. [Online]. Available: https://fda.gov/media/93971/download

[12] U.S. Food and Drug Administration, M9 Biopharmaceutics Classification System-Based Biowaivers: Guidance for Industry. Silver Spring, MD, USA: FDA, May 2021. [Online]. Available: https://fda.gov/media/148472/download

[13] U.S. Food and Drug Administration, Presentation on Patents and Exclusivity Under the FD&C Act and 21 CFR 314.108. Silver Spring, MD, USA: FDA. [Online]. Available: https://fda.gov/media/92548/download

[14] U.S. Food and Drug Administration, GDUFA Reauthorization Performance Goals and Program Enhancements, Fiscal Years 2023–2027 (GDUFA III Commitment Letter). Silver Spring, MD, USA: FDA. [Online]. Available: https://fda.gov/media/153631/download

[15] European Parliament and Council of the European Union, "Directive 2004/27/EC of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use," 2004. [Online]. Available: https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32004L0027

[16] Committee for Medicinal Products for Human Use, European Medicines Agency, Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/Corr. London, U.K.: EMA, Jan. 20, 2010. [Online]. Available: https://ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf

[17] R. K. Verbeeck and F. T. Musuamba, "The revised EMA guideline for the investigation of bioequivalence for immediate release oral formulations with systemic action," Journal of Pharmacy & Pharmaceutical Sciences, vol. 15, no. 3, pp. 376–388, 2012. [Online]. Available: https://journals.library.ualberta.ca/jpps/index.php/JPPS/article/download/11759/13883

[18] International Council for Harmonisation, ICH M9 Guideline on Biopharmaceutics Classification System-Based Biowaivers, Step 5, EMA/CHMP/ICH/493213/2018. Amsterdam, Netherlands: European Medicines Agency, Feb. 10, 2020. [Online]. Available: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m9-biopharmaceutics-classification-system-based-biowaivers-step-5_en.pdf

[19] European Parliament, "Deal on comprehensive reform of EU pharmaceutical legislation," press release, Dec. 11, 2025. [Online]. Available: https://www.europarl.europa.eu/news/en/press-room/20251209IPR32110/deal-on-comprehensive-reform-of-eu-pharmaceutical-legislation

[20] Council of the European Union, "'Pharma package': Council and Parliament reach a deal on new rules for a fairer and more competitive EU pharmaceutical sector," press release, Dec. 11, 2025 (updated Mar. 6, 2026). [Online]. Available: https://www.consilium.europa.eu/en/press/press-releases/2025/12/11/pharma-package-council-and-parliament-reach-a-deal-on-new-rules-for-a-fairer-and-more-competitive-eu-pharmaceutical-sector/

[21] Council of the European Union, "'Pharma package': Council adopts new rules for a fairer and more competitive EU pharmaceutical sector," press release, Sep. 28, 2026. [Online]. Available: https://www.consilium.europa.eu/en/press/press-releases/2026/09/28/pharma-package-council-adopts-new-rules-for-a-fairer-and-more-competitive-eu-pharmaceutical-sector/

[22] L. Amos-Stone, A. Roussanov, C. Schoonderbeek, A. Williams, and H. Jalil, "Provisional text of the political agreement on the reform to the EU regulatory framework for medicinal products is published," BioSlice Blog, Mar. 6, 2026. [Online]. Available: https://www.biosliceblog.com/2026/03/provisional-text-of-the-political-agreement-on-the-reform-to-the-eu-regulatory-framework-for-medicinal-products-is-published/

[23] Medicines and Healthcare products Regulatory Agency, "Types of application for marketing authorisations (legal basis of applications)," GOV.UK. [Online]. Available: https://www.gov.uk/guidance/types-of-application-legal-basis

[24] Medicines and Healthcare products Regulatory Agency, "Comparator products in bioequivalence/therapeutic equivalence studies," GOV.UK. [Online]. Available: https://www.gov.uk/guidance/comparator-products-in-bioequivalencetherapeutic-equivalence-studies-from-1-january-2021

[25] Central Drugs Standard Control Organization, New Drugs and Clinical Trials Rules, 2019: Notifications and Amendments. New Delhi, India: CDSCO. [Online]. Available: https://cdsco.gov.in/opencms/opencms/en/Acts-and-rules/New-Drugs/

[26] N. Sharma, T. Kukade, and M. Antani, "Cutting the red tape: Relaxed approval requirements for drug studies," Nishith Desai Associates, Mumbai, India, Jan. 30, 2026. [Online]. Available: https://www.nishithdesai.com/research-and-articles/hotline/pharma-healthcare-update/cutting-the-red-tape-relaxed-approval-requirements-for-drug-studies-15492