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COMPARISON OF GENERIC DRUG APPROVAL TIMELINES ACROSS MAJOR REGULATORY AGENCIES

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Abstract

Generic medicines account for most prescriptions dispensed in many countries, so the time they take to clear regulatory review has direct consequences for cost and access. This narrative review compares what the published literature and agency documents say about generic approval pathways and timelines in the United States, the European Union, Canada, the World Health Organization prequalification system and several developing regulatory systems. It describes how review clocks are defined, why elapsed time differs from statutory time, and which scientific and administrative factors lengthen review. Published comparisons are scarce, definitions are inconsistent and agencies rarely report like-for-like data. The review reports no new data and offers practical suggestions for more comparable reporting.

1. INTRODUCTION

Generic medicines are the workhorse of modern prescribing. In the United States they fill the large majority of prescriptions, and in most European markets their share by volume is comparably high, although the share by value is far smaller [1, 2, 3]. The reason is price. Once patents and exclusivities lapse, competition among several manufacturers pushes prices down sharply, which is why health systems depend on a steady flow of new generic approvals to contain spending [1, 4].

Speed matters in that process. Every month a generic product waits in review after the originator's protection ends is a month in which the brand price stands, so regulatory timelines have a measurable economic meaning [2, 4]. The modern framework in the

United States dates from the Hatch-Waxman legislation of 1984, which created the abbreviated pathway that lets a manufacturer rely on the originator's safety and efficacy data and demonstrate instead that its product is pharmaceutically equivalent and bioequivalent [5, 6]. Other jurisdictions built comparable abbreviated routes, with their own vocabulary and their own clocks [7, 8, 9].

Comparing those clocks is harder than it sounds. A statutory review period, a performance goal, the time an application sits with the agency and the time between submission and marketing authorisation are four different quantities, and published sources use the terms loosely. Agencies also differ in whether the applicant's response time counts. A fair comparison therefore needs a clear definition before any number is quoted, and the first aim of this review is to supply one [10, 11, 12].

The question carries wider significance than administrative tidiness. Regulators in high-income settings have large generic review programmes, but many countries have small agencies with limited staff, and long queues there delay access to affordable treatment [13, 14, 15]. The remaining sections describe the pathways, what the timelines measure, what slows them down, how scientific requirements differ, and what can be said about effects on access. Put simply, an approval delayed in one place is often a medicine unavailable in another.

The scope here is deliberately limited. The review concerns small-molecule generic medicines for human use that are submitted through abridged applications in the major regulatory systems. Biosimilars, over-the-counter switches, veterinary products and post-approval variations follow different rules and different clocks, and they are left aside. Fixed-dose combinations and so-called complex generics, such as inhalers, long-acting injectables and topical products, are mentioned where they change the timeline, because they often cannot rely on a simple pharmacokinetic study in healthy volunteers [10, 16, 17].

Terminology also varies across countries. What is called a generic in the United States may be a multisource product in WHO documents, a duplicate in some national systems and a hybrid application in Europe when a product differs slightly from its reference. These labels matter for timelines because each category triggers a different data package and, sometimes, a different review stream [7, 9]. Readers should check how a source defines its terms before drawing conclusions.

2. REGULATORY PATHWAYS

In the United States, a generic applicant files an abbreviated new drug application. The applicant must show that the proposed product has the same active ingredient, strength, dosage form and route as the reference listed drug, and that it is bioequivalent, usually through a pharmacokinetic study in healthy volunteers [6, 18]. Approved products receive a therapeutic equivalence rating in the Orange Book, which pharmacists and prescribers use to judge substitutability [19]. The application also includes manufacturing, stability and impurity data to the same standards applied to innovator products [20], and general accounts of the approval process describe how such evidence is assembled and reviewed [21].

Filing is a stage in its own right. A US application must pass a receipt and filing review before substantive assessment begins, and an application that is incomplete can be refused at that point without scientific evaluation [10, 18]. Fees under the user-fee programme are paid on submission and again each year for facilities and products, so the cost of a failed first attempt falls on the applicant [10, 22]. Dossiers follow the Common Technical Document structure, with quality information in module 3 and the bioequivalence report in module 5, so much of the work of preparing a US application can be reused elsewhere [23].

European arrangements are more layered. A generic can reach the market through the centralised procedure run by the European Medicines Agency, through national authorisation, or through the mutual recognition and decentralised procedures in which one member state acts as reference state and others recognise its assessment [7,

8]. The underlying legal basis is the same abridged application in the pharmaceutical code, which allows reference to the originator's dossier after the data protection period has run [7]. Which route a company picks depends on market strategy and the product type as much as on science.

Protection periods in Europe are written into the pharmaceutical code. An originator receives eight years of data exclusivity, during which a generic applicant cannot refer to its file, followed by two years of market protection during which an authorised generic cannot be sold, with a possible extra year for a new indication of significant benefit [7]. The generic dossier can therefore be submitted before the product can be marketed, and the timing of an approval relative to market protection is part of company planning. Authorisation may be granted early, but launch waits for the protection period to end [7, 8].

Canada, Australia, Japan and several other agencies run abbreviated pathways too, each with a defined set of bioequivalence expectations. Health Canada, for example, publishes detailed guidance on comparative bioavailability studies and has long accepted certain waivers for highly soluble, rapidly dissolving products [24, 25]. Differences in what is permitted at the margins, such as the handling of highly variable drugs and the acceptance range for narrow therapeutic index drugs, create regional variation in the dossier that must be assembled [18, 26, 27].

At the global level, the WHO Prequalification Programme assesses generic products intended mainly for procurement by United Nations agencies, and its guidance on multisource products sets out interchangeability requirements that many national authorities in lower-income countries now adopt [9]. The system works partly by reliance. A national regulator can use a stringent authority's assessment or a prequalification decision as a basis for its own decision, shortening review while retaining responsibility for the final authorisation [14, 15, 28].

Agencies that are smaller or younger than the FDA and EMA often model their systems on those of the larger bodies. The choice between full independent review, abridged review and recognition of another authority's decision depends on local capacity, legislation and risk tolerance. Historical accounts of regulatory development show a steady move toward risk-based, collaborative models, with reliance and work-sharing increasingly seen as a rational use of limited assessor time [14, 15, 28]. These choices have a greater influence on elapsed time than the details of any one agency's checklist.

Intellectual property rules deserve a final note. Patent linkage, under which approval or launch is connected with patent status, exists in the United States and several other countries but not uniformly in Europe, so the same generic may face different obstacles in different places even when the scientific review is complete [4, 5, 6, 29]. This is one of the reasons the order and timing of launches across regions look uneven.

Common dossier structure helps. The Common Technical Document format agreed through the International Council for Harmonisation organises quality, nonclinical and clinical information the same way for the United States, European Union and Japan, and many other regions have adopted it [23]. Format harmonisation is not the same as requirement harmonisation, but it reduces the work of re-formatting and makes it easier for assessors to find what they need.

Not every route is equally available. Small markets without the capacity for independent assessment may rely on abridged or verification-only procedures, and the quality of the dossier received then matters a good deal. In those settings a shorter nominal review does not necessarily mean a lighter scientific burden; it may reflect trust placed in another authority's work [14, 15]. Patent challenge incentives similarly differ between legal systems [4, 29].

3. WHAT THE TIMELINES MEASURE

Taking the United States first, the Generic Drug User Fee Amendments introduced in 2012 tied industry fees to agency performance goals, and the second reauthorisation set a goal of reviewing most standard original applications within 10 months of submission [10, 22]. That is a

target for the agency's own action. It does not capture applicant response time, and an application that receives a complete response letter must be resubmitted and reviewed again. Total time to approval therefore often exceeds the headline goal by a wide margin, especially for first-cycle failures [10]. Where a first-cycle approval is achieved, however, the process can be considerably quicker than the average [10].

A workable definition of the clock needs several time points. These include the date of first submission, the date an application is validated, the date of each query sent to the applicant and each response received, the date of the decision, and the date a product can be placed on the market once national pricing and reimbursement steps are complete. Agency time is the sum of the periods in which the file sits with the regulator, applicant time is the sum of the periods in which it sits with the company, and total time is the sum of both [8, 10, 11]. Reports that merge them make agencies look faster or slower for reasons unrelated to efficiency.

European figures work differently. Procedural timetables for the decentralised procedure and the centralised procedure are expressed as active days, typically about 210 for the assessment phase, with clock-stops when the authority sends a list of questions and the applicant prepares answers [7, 8]. Elapsed calendar time is longer than the active-day count, and national phases that follow the European assessment, including pricing and reimbursement decisions, add more. Comparing 210 active days with 10 calendar months therefore compares unlike things [8, 11].

Other agencies report percentages of applications decided within target periods, median times for completed reviews or simple counts of approvals per year. A few publish regular performance reports. Many do not, and transparency itself varies, as studies of public assessment reports in Europe and Australia have shown [30]. Without a shared definition of the start and stop of the clock, the measure that most readers care about, the calendar time from first submission to the point at which a product can be sold, is rarely available in a form that allows comparison [11, 12].

The best comparative work in the published literature concerns novel medicines. Studies comparing European and American decisions on new active substances found that the two agencies reached the same decision in the great majority of cases, and that differences in time often traced to differences in procedure and in the use of expedited pathways more than to scientific disagreement [11, 12]. The authors of these studies caution that decision timing is affected by company strategy about where to file first. Whether the same holds for generics is plausible but unproven, since generic applicants tend to file in several regions at once and usually follow the originator's lead [11, 12].

The main pathway features and published points of comparison are summarised in table 1, grouped by jurisdiction and cross-cutting theme, and the way the entries divide between groups is shown in fig. 1. The table is deliberately qualitative: it records what each source states about the pathway, its clock and its scientific requirements, and it avoids numbers that cannot be tied to a published source. It is also worth remembering that it describes the position up to 2021 and that the agencies have been revising procedures continually [10, 11].

Table 1: Published features of generic approval pathways and timelines by jurisdiction

Pathway or issue	Reported feature	Ref.
US abbreviated application Hatch-Waxman route	Relies on the reference product's data; requires pharmaceutical equivalence and bioequivalence rather than new clinical trials.	[5, 6, 18]
US performance goals	User-fee reauthorisation sets review goals for most standard applications; goals cover agency action, not applicant response time.	[10, 22]
Therapeutic equivalence listing	Orange Book ratings guide pharmacy substitution of approved products.	[19]
EU decentralised and mutual recognition	One reference member state assesses; others recognise; timetable counted in active days with clock-stops.	[7, 8]

Pathway or issue	Reported feature	Ref.
EU bioequivalence guideline	Allows widened peak-concentration limits for highly variable drugs under defined conditions.	[26]
Health Canada comparative bioavailability	Detailed study and analysis expectations; waivers for qualifying immediate-release products.	[25]
WHO multisource guidance	Interchangeability requirements adopted by many national regulators; used in prequalification.	[9]
Regulatory capacity in Africa	Limited staffing and laboratory capacity lengthen queues; reliance and regional collaboration proposed.	[14, 15]
Common Technical Document	Shared dossier format across ICH regions reduces re-formatting work.	[23]
BCS-based biowaivers	Class I accepted by FDA, EMA and WHO; class III and dissolution criteria differ.	[24]
Narrow therapeutic index drugs	US approach uses tighter limits and replicate designs; European expectations differ in detail.	[27]

4. SOURCES OF DELAY

Applications are not rejected at random. In the United States, deficiencies cluster in a few areas that agency officials have described in public presentations and journal articles: bioequivalence study design and statistics, drug substance quality and impurity control, manufacturing facility compliance, and labelling [16, 17, 31]. Failure at the first cycle is common enough that the number of review cycles is probably the strongest single predictor of total time to approval, and it is the quantity a sponsor can influence most through dossier quality [10, 17]. Agency officials have also pointed to the quality of the active pharmaceutical ingredient, often made by a separate firm, as a source of avoidable questions [16, 20].

Bioequivalence deficiencies deserve separate mention because they are both frequent and avoidable. Common problems described in the literature include inadequate washout, a sample size that leaves the study underpowered, unvalidated or poorly documented bioanalytical methods, protocol deviations that are not justified, and the use of a reference product that does not match the listed one [18, 31, 32]. A study that fails or is rejected on design grounds usually has to be repeated, which adds months to the plan, and a repeated human study costs far more than getting the first design right. Regulators encourage sponsors to seek advice before starting pivotal studies.

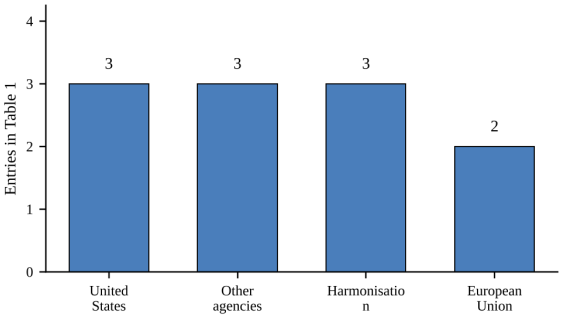


Fig. 1: Number of entries in table 1 by jurisdiction or theme

Quality-by-design thinking was promoted for generics in the late 2000s, in the belief that applicants who understood their formulation and process well would submit better-supported applications and trigger fewer questions [16, 17]. The ideal is a dossier in which critical quality attributes, a justified specification and a development rationale are visible from the start. In practice, the extent to which generic applications adopted this approach varied, and published evidence of a measurable effect on review time is thin [17].

Communication channels with the agency influence outcomes. Under the US user-fee arrangements, applicants may submit controlled correspondence to ask about drug-specific scientific issues, and product-specific guidances set out recommended study designs for many reference products [10, 16]. Pre-submission meetings are available in Europe for some product types, and scientific advice procedures exist at national level [8, 26]. Applicants who use these channels are better placed to submit a complete first-cycle application, though the evidence is mostly the testimony of regulators and consultants, not controlled comparison.

Facility inspections add a separate time element. A product can be scientifically acceptable and still wait for a pre-approval inspection, and when manufacturing sites are overseas the scheduling is complicated by travel and by the number of sites in the supply chain. The same is true in Europe, where inspections are coordinated across member states and may involve third-country sites [8]. Delays of this kind are seldom included in published comparisons because they sit outside the nominal review clock.

Patents and exclusivities interact with timing too. In the United States, an approval can be tentative until a patent expires or litigation is resolved, and 180-day exclusivity for the first filer is a deliberate incentive to be early [4, 5, 6]. In Europe the combination of data protection and market protection periods defines when a generic dossier may reference the originator's file and when it may be marketed [7]. In that sense the approval timeline and the commercial timeline are linked but not identical, and strategies for patent challenge and settlement have been critiqued by economists and lawyers for slowing entry [1, 29, 33].

Formulation changes during review are a further, quieter cause of delay. A company may need to alter a dissolution method, tighten a specification or change a manufacturing site after receiving questions, and each change can require supporting stability data that take months to generate [20]. Planning for these contingencies inside the development programme, for example by running long-term stability studies in parallel with the pivotal study, is a common way of shortening the post-submission phase.

Resource constraints, finally, shape the picture outside the large agencies. Surveys of regulators in Africa and other low- and middle-income regions describe understaffed assessment units, limited laboratory capacity and dependence on paper-based systems, each of which lengthens queues independently of the science [14, 15]. Reliance pathways and regional collaboration are the usual responses. Where the same inspectorate also supervises licensing of wholesalers and hospitals, generic reviews compete for inspection time with unrelated duties.

5. SCIENTIFIC AND HARMONISATION ISSUES

Bioequivalence is the centre of the generic dossier, and the way it is judged shapes both timelines and trust. The usual criterion is that the 90% confidence interval for the ratio of geometric means of area under the curve and peak concentration falls within 80.00 to 125.00%, tested in a crossover study in healthy adults [18, 26, 32]. A review of more than a decade of data submitted to the US Food and Drug Administration found that approved generics differed from the reference product by small amounts, on average well within the acceptance limits [31]. Clinical comparisons for cardiovascular drugs found no evidence of inferiority for generics [34].

Highly variable drugs show why statistics matters. When within-subject variability exceeds about 30%, a standard crossover design needs a large number of volunteers to demonstrate bioequivalence with the conventional limits, and sponsors may be tempted to enrol far more subjects than is ethical or practical [26, 32]. Reference-scaled and widened-limit approaches were introduced to deal with this, but they require replicate designs, prespecified statistical methods and a justification that the variability is a property of the drug and not of the formulation [18, 26, 32]. The need to fulfil different statistical expectations is a recurring reason for rework in dossiers aimed at several regions.

Regional differences do remain. The European guideline allows widened limits for peak concentration in highly variable drugs under defined conditions, while US guidance asks for reference-scaled average bioequivalence with replicate designs; narrow therapeutic index drugs attract tighter limits in the United States, though the details differ from European expectations [18, 26, 27]. Each divergence forces companies that market in both regions to run additional studies or to design one study that satisfies both, which in turn lengthens development and may lengthen review [27, 32].

Biowaivers offer a shortcut in suitable cases. Under the Biopharmaceutics Classification System, immediate-release products containing highly soluble, highly permeable

drugs can be approved on dissolution data alone, and WHO, EMA and FDA all provide such a route. A comparison of the three sets of requirements found that class I drugs are accepted by all, but that class III drugs and the exact dissolution criteria are treated differently [9, 24]. Applicants must therefore check each agency's list of eligible substances before assuming one dossier will work everywhere.

Complex generics are where the regulatory timelines are least predictable. For locally acting products such as orally inhaled drugs, nasal sprays, topical dermatological formulations and ophthalmic emulsions, plasma concentrations may not reflect delivery to the site of action, so equivalence may rest on in vitro characterisation, pharmacodynamic studies or clinical endpoint studies [16, 17]. Research programmes in the United States were set up to develop alternative methods, and the rate of approval for such products has historically been lower than for oral solid doses. Reviews are longer, deficiency rates are higher and applicant experience is less established [10, 16, 17].

Post-approval surveillance completes the picture. Approval of a generic does not end the regulator's interest: variations to the manufacturing process, new suppliers of the active ingredient and signals from pharmacovigilance all continue to be assessed, and quality defects in generic products have prompted recalls in several regions [31, 33, 34]. Strong post-market oversight is what allows abbreviated review to be trusted in the first place. Agencies that speed approval without investing in inspections and surveillance risk eroding the confidence on which generic substitution depends [14, 28, 33].

Stability and impurity expectations are on the whole better harmonised than bioequivalence expectations, thanks to ICH guidelines on stability testing and on impurities in new drug substances, which are applied to generics as well [20]. Remaining differences tend to concern climatic zone requirements, the number of batches and the treatment of nitrosamine-type contaminants, which arrived as a regulatory issue as recently as 2018 and led to a wave of questions to generic applicants [20].

A practical limit on all of this is the reference product itself. When originator products differ between markets, as sometimes happens with formulations or strengths, a generic may need to be compared against a locally sourced reference, or against a reference from another market with proof that the two are the same. The WHO interchangeability guidance addresses this through its comparator product lists [9], though national implementation is variable.

6. IMPLICATIONS FOR ACCESS

What do timelines mean for patients? Economic work from the United States and Europe shows that market entry by multiple generic suppliers drives prices down in a dose-response fashion: the more entrants, the lower the price, with the largest fall arriving when several enter together [2, 3, 4]. Faster review can bring forward that point, and also reduces the chance that a brand manufacturer extends its monopoly through product switching or other lifecycle strategies [1, 2, 33].

Hospital and community pharmacy practice feeds back into the system. Substitution rules, tendering and reference pricing determine how quickly an approved generic reaches patients, and those rules are set by health ministries and payers rather than by medicines regulators [3, 13, 35]. A product approved in record time may still sit unused if substitution is not permitted or if prescribers prefer brand names. Pharmacists who can explain what an approval rating means, and who understand that bioequivalence limits are applied to a ratio of means rather than to individual patients, are well placed to address doubts at the point of care [19, 36].

Acceptance of generics depends on trust in the regulatory system. Surveys of physicians have found scepticism about generic drugs in some settings, driven partly by concerns about quality and partly by unfamiliarity with how equivalence is demonstrated [36]. Transparent assessment reports and clear Orange Book-type listings can help, and policies that promote generic use in low- and middle-income countries have worked best when they paired regulatory quality assurance

with pricing and prescribing incentives [13, 19, 35, 37]. Speed gained through weaker scrutiny would undermine that trust.

Supply is the other side of the access question. A market with thin margins can lose manufacturers, and an approval that arrives quickly but is followed by market exit does little for patients. Analyses of generic competition suggest that very low prices, particularly for older sterile injectables, are associated with fewer suppliers and a higher risk of shortage, so regulators and payers increasingly consider sustainability alongside price [1, 2, 3, 37]. From this angle, predictable review and reasonable fees serve patients as much as the headline speed of any individual application.

Wider societal benefits include sustained access for patients with chronic conditions, freeing resources for newer drugs, and greater supply security when several manufacturers serve a market [35, 37]. Those benefits depend on approval decisions being not just fast but predictable, so that manufacturers can plan investment.

7. LIMITATIONS AND FUTURE DIRECTIONS

The main limitation is the evidence base. Few peer-reviewed papers deal with generics specifically, most comparisons concern novel therapeutics, and agency documents differ in definition and coverage [11, 12, 30]. Statements about relative speed between agencies therefore rest on weak foundations, and anyone using such statements to plan filings should confirm the current position directly with each authority. The pace of procedural change is a further reason for caution, because guidance issued in one year may be superseded in the next [10]. Even within a single agency, the mix of products changes from year to year, with simple oral solids giving way to more complex dosage forms, so a fall or rise in median review time may reflect case mix and not performance [16, 17].

Several steps would improve matters. Agencies could report the median calendar time from first submission to final decision, split into agency time and applicant time and by number of review cycles. Independent researchers could then compare agencies on a common basis. Regulators could also go further in aligning bioequivalence requirements for highly variable and narrow therapeutic index drugs and in recognising each other's inspections and assessments [18, 26, 27, 28]. Capacity building in smaller agencies, linked to reliance, offers probably the greatest gain in access per unit of effort [14, 15].

Electronic submission and structured data are likely to change the picture. The eCTD format is already standard in the major regions, and structured product and quality information may make it easier for assessors to find relevant data and for agencies to monitor their own performance [23]. Work-sharing among European authorities and collaborative assessment initiatives elsewhere also point towards a model in which one detailed assessment supports several national decisions [8, 28]. If those developments continue, comparisons of national clocks will matter less than comparisons of how quickly a single high-quality assessment can be shared and used.

8. CONCLUSION

Generic approval timelines are real and consequential, but they are less comparable than headline figures suggest. Statutory periods, performance goals, active-day counts and elapsed calendar time measure different things, and the main drivers of delay, notably repeated review cycles, inspection scheduling and patent-related timing, sit partly outside the nominal clock [10, 11, 12].

Scientific requirements are broadly convergent for quality and moderately divergent for bioequivalence of difficult drug classes [24, 26, 27]. Access gains are likely to come from better dossiers, reliance among agencies and stronger regulatory capacity in smaller systems, along with consistent public reporting that allows fair comparison [14, 15, 28, 30].

9. ABBREVIATIONS

ANDA-Abbreviated new drug application, BCS-Biopharmaceutics Classification System, CTD-Common Technical Document, EMA-European Medicines Agency, FDA-Food

and Drug Administration, GDUFA-Generic Drug User Fee Amendments, ICH-International Council for Harmonisation, WHO-World Health Organization, EU-European Union

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All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

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