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REGULATORY PATHWAYS FOR GENERIC ANTIVIRAL DRUGS: ANDA REQUIREMENTS IN THE USA COMPARED WITH BRICS

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Abstract

Generic antiviral medicines widened access to treatment for chronic and epidemic viral infections once patents on branded products expired. Approval requirements for generic medicines differed between countries, and earlier comparisons either described frameworks that were later replaced or gave little attention to antiviral-specific bioequivalence expectations. This study compares the abbreviated new drug application pathway of the United States Food and Drug Administration with generic drug registration in Brazil, Russia, India, China and South Africa, and it illustrates product-specific bioequivalence expectations for two antivirals, acyclovir topical cream and oseltamivir phosphate capsules. The novelty of the study lies in combining country-level procedures with antiviral case studies and in correcting superseded descriptions found in earlier compilations. The work is a descriptive comparative review. Regulatory instruments, regulator publications, product-specific guidances and published comparative studies are compiled, and six parameters (regulator, legal basis, dossier format and language, review structure, bioequivalence approach and indicative review duration) are tabulated for each country. Time-sensitive items are checked against notices current in November 2026. No statistical analysis is applicable to this descriptive study. All six jurisdictions use a dossier organised on the Common Technical Document and require proof of bioequivalence to a reference product, but they differ in legal basis, language, review structure, reliance on assessments by other regulators, patent-linkage mechanisms and reported review duration. Earlier descriptions are superseded in several respects: the Chinese and South African regulators have been renamed, Russia registers medicines under Eurasian Economic Union rules, the Brazilian generic requirements are consolidated in a 2022 resolution, and the Indian rules of 2019 replaced Schedule Y. The acyclovir case shows that a topical product can be approved through formulation sameness with in vitro release testing or through a clinical endpoint study, whereas the oseltamivir case shows that an oral capsule can be approved through a biowaiver based on the Biopharmaceutics Classification System or through fasting and fed crossover studies. Convergence on the Common Technical Document and on bioequivalence principles lowers the barrier to multi-country filing, but national legal instruments, language, timelines and product-specific expectations still require a jurisdiction-specific strategy.

Keywords: *Abbreviated new drug application; Generic antiviral drugs; Bioequivalence; Drug registration; Acyclovir; Oseltamivir phosphate; Regulatory affairs; BRICS countries; Common Technical Document.*

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INTRODUCTION

Viral infections range from self-resolving illness to acute fatal disease, and antiviral drugs are the main tool for treating them. By April 2016, 90 antiviral drugs in 13 functional groups had been formally approved for nine human infectious diseases [1]. Antiviral strategies target either viral functions, such as nucleic acid polymerases, proteases, integrases and neuraminidases, or host-cell functions that the virus requires (Figure 01) [2].

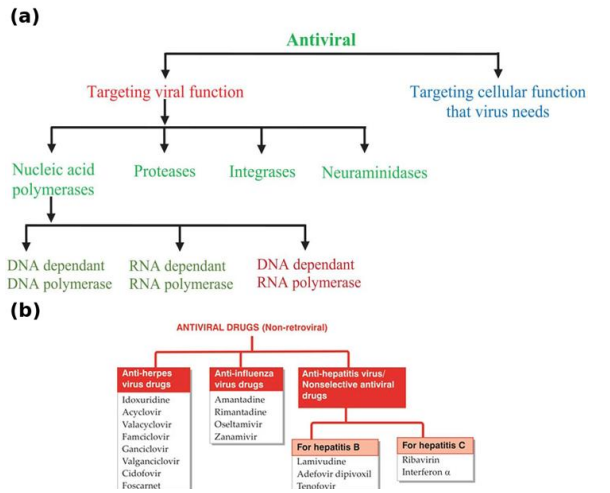


Figure 01: Common inhibitory actions (a) and classification of non-retroviral antiviral drugs (b). Reproduced from the authors' dissertation.

Generic versions of a branded antiviral can enter the market once its patents and regulatory exclusivities expire. A generic product contains the same active ingredient as the innovator product, and its approval rests on showing pharmaceutical equivalence and bioequivalence instead of repeating the innovator's preclinical and clinical programme [3,4]. In the United States, the Drug Price Competition and Patent Term Restoration Act of 1984, known as the Hatch-Waxman Amendments, created this abbreviated pathway.3 Bioequivalence is generally shown by comparing the rate and extent of absorption of the generic and reference products [5].

Regulatory requirements for generics differ between countries. A company therefore cannot simply develop one product and submit it everywhere, and the regulatory strategy should be settled before development starts [6]. Earlier work compared generic registration requirements globally [7]. Another study compared the United States, Europe and India [8]. A further study compared the United States and Canada [9]. The registration of generic drugs in China was reviewed separately [10]. The registration and approval of generics was also compared across the five founding BRICS countries (Brazil, Russia, India, China and South Africa) [11]. Reviews of generic development add that the choice of target market affects excipient grade, test methods and stability design [12].

Among the studies identified for this work, few place antiviral-specific bioequivalence expectations beside country-level procedures, and some describe regulators and rules that have since changed. This matters because the United States Food and Drug Administration publishes product-specific guidances that recommend how to demonstrate bioequivalence for individual antivirals [13,14]. A developer who targets several countries needs to know how far such guidance can be carried across borders and which national requirements still apply. The matter is also commercially relevant, because market analysts expect several branded antivirals to lose patent protection in the coming years, which widens the market for generic versions [15].

The aim of this study is to compare the abbreviated new drug application pathway of the United States with the generic drug registration frameworks of Brazil, Russia, India, China and South Africa. The objectives are (i) to describe the review structure of the United States pathway, (ii) to compare the six countries on regulator, legal basis, dossier format and language, bioequivalence approach, review structure and indicative review duration, (iii) to illustrate product-specific bioequivalence expectations with acyclovir topical cream and oseltamivir phosphate capsules, and (iv) to identify descriptions in earlier compilations that current instruments have superseded.

2. MATERIALS AND METHODS

2.1. Study Design, Location and Period

A descriptive comparative review of regulatory requirements was carried out. Only published documents were used. The study involved no human participants, animals, patient data or laboratory experiments, so ethics committee approval was not required.

2.2. Selection of Jurisdictions

The United States was chosen as the reference jurisdiction because the Food and Drug Administration publishes product-specific bioequivalence guidance for antivirals.13,14 Brazil, Russia, India, China and South Africa, the five founding members of the BRICS group, were chosen as comparators, following an earlier comparative study of this group [11].

2.3. Sources of Regulatory Information

Sources were assigned to each jurisdiction before data extraction. For the United States, the sources were the abbreviated new drug application page of the Food and Drug Administration, the Hatch-Waxman Amendments, Parts 314 and 320 of Title 21 of the Code of Federal Regulations, the commitment letter for the third authorisation of the Generic Drug User Fee Amendments, and the Federal Register notices on fee rates for fiscal year 2027 and on reauthorisation [3-5,16-19]. For Brazil, the sources were the law that created the generic category and Resolution RDC 753 of 2022 [20,21]. For Russia, the sources were the Eurasian Economic Commission Council decisions on registration rules and on bioequivalence rules, together with a law-firm bulletin on the transition period [22-24]. For India, the sources were the New Drugs and Clinical Trials Rules, 2019, and a circular on approval of subsequent applicants as reported in trade press [25, 26]. For China, the source was a consultancy summary of the 2025 acceptance guidelines for chemical drug registration [27]. For South Africa, the sources were the backlog clearance strategy of the regulator and a published assessment of generic registration timelines [28,29].

Secondary literature was used for dossier content, review durations and fees reported for the comparator countries [6-12].

2.4. Regulatory Provisions Examined

2.4.1. United States

The regulator is the Food and Drug Administration. The dissertation records the following requirements. Applications for new drugs and generics are submitted in electronic form and compiled according to the Code of Federal Regulations (21 CFR Parts 314 and 320); three application types are recognised, namely new drug applications, abbreviated new drug applications and biological applications.3-5,16 The applicant files directly or through a United States agent whose appointment letter is placed in Module 1 (item 1.3.1.2). The administrative set comprises the cover letter, Form 356h, the application form, the field copy certification (1.3.2), the debarment certification required by the Generic Drug Enforcement Act of 1992 (1.3.3), the financial certification and disclosure for clinical investigators on Form 3454 (1.3.4), and patent and exclusivity information with the patent certification (1.3.5). Documents are prepared on 8.5 x 11 inch pages in Times New Roman 12 point, with 8-10 point type permitted in tables. Labelling comprises package inserts, container and carton labels that match those of the reference listed drug (RLD), annotated draft labelling and a side-by-side comparison with the RLD labelling (1.14.1-1.14.3), and a risk management plan or the risk evaluation and mitigation strategy of the RLD where applicable (1.16.1-1.16.2). Module 1 also carries the statement of right of reference to each drug master file (1.4.2), the basis for submission (1.12.11), evidence that the product is the same as the RLD (1.12.12), the environmental assessment or request for categorical exclusion (1.12.14) and any request to waive in vivo bioavailability or bioequivalence evidence (1.12.15).

For quality, the dissertation notes a statement of residual solvent limits for the drug substance and excipients under the United States Pharmacopeia; in Section 3.2.R, the names and sites of suppliers and manufacturers of raw materials and packaging components, with access letters excluded from that section and the certificates on bovine and transmissible spongiform encephalopathy placed with the drug master file; and executed batch records, comparability protocols and method validation packages (3.2.R.1-3.2.R.3). Every application must be in electronic Common Technical Document format with structured product labelling and study tagging files, and the dissertation states that no paper format is accepted. The review sequence in Figure 2 begins with receipt of the application, a checklist review by a consumer safety technician and a compliance decision, after which the application is distributed for review. The dissertation states a 60-day interval after the compliance decision; this interval was not verified and is not used in the comparison. The Generic Drug User Fee Amendments of 2012 are recorded as the means of funding inspections and application review so as to reduce the backlog and speed review; the fee of US$76,030 given for that period is superseded (Table 3) [17,18].

2.4.2. Brazil

The regulator is the National Health Surveillance Agency (ANVISA), a member of the International Council for Harmonisation. The dissertation records that companies must register with ANVISA before they can use the electronic submission platform; that dossiers follow the Common Technical Document and are translated into Portuguese; that a registration lasts five years; and that imported products need a letter of clearance and a certificate of pharmaceutical product from a major market. After the dossier is examined and queries are issued, the sponsor has 30 days to reply, and the final decision rests with the Board. The dissertation gives 400 days as the typical period for a new chemical entity and 180 days as the maximum for a priority application, and it recommends local clinical trials; these durations concern new chemical entities and were not carried into the generic comparison. Prices and their annual adjustment are set by the Medicines Market Regulation Chamber (CMED). Registration categories are medicinal products, pharmaceutical raw materials and health products. Generic medicines were introduced by Law 9,787 of 1999, and Resolution 391/1999 set their technical requirements in the same year; pharmaceutical equivalence and bioequivalence studies are required to show that the generic is stable and therapeutically equivalent to the reference medicine. Resolution RDC 73/2016 governs post-registration changes and cancellation. Resolution 391/1999 is superseded by RDC 753/2022 (Table 03) [20,21].

2.4.3. Russia

The dissertation names the Federal Service for Surveillance in Healthcare (Roszdravnadzor) as the body that decides and issues the registration certificate, the federal state expert institution for pharmaceuticals as the evaluating body, and the Ministry of Health as the body that sets the policy on development, quality and distribution of medicines, with the federal service holding control and supervisory duties. Its flowcharts present the registration and approval of a generic as a sequence of submission, expert evaluation and certificate issue. Since 1 January 2021 registration follows the Eurasian Economic Union rules of Decision 78 of 2016, bioequivalence studies follow Decision 85 of 2016, and national certificates ended no later than 31 December 2025, so the national procedure described in the dissertation is treated as superseded [22-24].

2.4.4. India

The regulator is the Central Drugs Standard Control Organisation (CDSCO). The dissertation records that registration papers must include Schedule Y and a report of the clinical trials; that under Rule 122A of the Drugs and Cosmetics Rules, 1945, the licensing authority may approve import of a new drug on the basis of trials done in other countries, and may permit trials in India to be waived where the drug is already licensed and in long use elsewhere; that for drugs discovered abroad the applicant submits the documents from other countries and the authority

may require repetition of studies, with an option to proceed from phase 3; and that clinical study requirements vary from case to case with the authority's confidence in the safety and efficacy profile. Two inspection instruments are also recorded: the notice of 6 August 2014 (File No. QA/RI/NRA/Compliance Report/63/14), which standardised inspection of manufacturing sites by State Drug Controllers (inspections of two to five days according to site size, priority to shelf-life determination, validation and prompt recall of non-compliant goods, prompt regulatory action and reporting), and the rule of November 2017 (F. No. 7-5/2017/DCG(I)/MISC(099)) on joint inspections by CDSCO and State inspectors. Schedule Y and Rule 122A are superseded by the New Drugs and Clinical Trials Rules, 2019 [25].

2.4.5. China

The dissertation names the State Food and Drug Administration (SFDA) and the China Food and Drug Administration (CFDA), the latter reorganised at ministerial level as the agency responsible for drugs, food, cosmetics and health food. Registration papers are sent in the Common Technical Document format. Review of all test documents by the Center for Drug Evaluation is recorded as taking 40 to 160 business days depending on the substance, clinical and bioequivalence data are submitted to the agency before approval, and an application whose clinical study is found unnecessary proceeds to the final round of registration. These agency names are historical; the National Medical Products Administration and its Center for Drug Evaluation now hold these roles [27].

2.4.6. South Africa

The dissertation names the South African Health Products Regulatory Authority (SAHPRA) as regulator of health products for humans and animals, with licences required for manufacture, wholesale and distribution of medicines, medical devices and radiation-emitting products. It then lists twelve registration and control requirements attributed to the Medicines Control Council (MCC): (1) claims for use, stated in a package insert; (2) registration based on those claims and the supporting scientific and clinical evidence; (3) specifications and controls for all inputs and the finished dosage form in its retail pack; (4) production methods and in-process controls; (5) a programme validating all parts and processes; (6) a Site Master File for the manufacturing site; (7) results of pharmaceutical, animal and human tests for new medicines; (8) studies may be done anywhere but are reviewed before registration; (9) a generic applicant must show the same therapeutic effect as the reference product; (10) advertising limited to the claims in the approved package insert; (11) self-regulation of promotion, with a code of conduct of the industry association for promotion to health workers; and (12) evaluation of dossiers to confirm they are kept up to date and approval of the facility where the medicine is made, tested and packed. The MCC was replaced by SAHPRA in 2018, so these requirements are read as historical and compared with the current routes [28, 29].

2.5. Parameters Compared and Data Extraction

Six parameters were extracted for each jurisdiction into a standard grid: the regulator, the principal legal basis, the dossier format and language, the stages of review, the approach to bioequivalence, and the indicative review duration. Notable recent changes were recorded as a seventh item. Terms were taken as they appear in the source documents. The regulators and instruments named in the dissertation were compared line by line with the current instruments, and every difference was recorded.

2.6. Dossier Structure

Dossier content was described using the five-module organisation of the Common Technical Document of the International Council for Harmonisation [30].

The dissertation's ANDA checklist for the electronic format was used to map the content of each module. Module 1 holds the forms and cover letter (item 1.2, including controlled correspondence and meeting minutes with the agency), administrative information (1.3), references (1.4.2, 1.12.4, 1.12.11, 1.12.12, 1.12.14, 1.12.15), labelling (1.14) and risk management (1.16). Module 3 holds the drug substance (3.2.S: general information, manufacture, characterisation, control, reference standards, container closure and stability) and the drug product (3.2.P: description and composition, pharmaceutical development, manufacture, excipient control, product control, reference standards, container closure and stability), the appendix on adventitious agents for sterile products (3.2.A.2) and regional information (3.2.R). Module 5 holds the tabular listing of clinical studies (5.2), comparative bioavailability and bioequivalence reports (5.3.1.2), in vitro-in vivo correlation reports (5.3.1.3) and bioanalytical and analytical method reports (5.3.1.4).

2.7. Antiviral Case Studies

Acyclovir topical cream and oseltamivir phosphate oral capsules were examined as examples of a locally acting topical product and a systemically acting oral product. The product-specific guidance of the Food and Drug Administration for each product was used to extract the recommended study options, conditions for in vitro or waiver routes, study designs, analytes and dissolution requirements.13,14 The waiver route for oseltamivir was read alongside the harmonised guideline on biowaivers based on the Biopharmaceutics Classification System [31].

The two case studies were chosen because they sit at opposite ends of the bioequivalence spectrum: acyclovir cream acts at the skin and cannot be assessed by plasma concentrations, while oseltamivir capsules act systemically and can. For each product, the guidance summary in the dissertation was read item by item and recorded under the same headings: active ingredient, dosage form and route, recommended studies, criteria for each option, study design, subjects, analytes, basis of the 90% confidence interval, strengths eligible for a waiver, and dissolution method. For the

acyclovir in vitro option, the supporting conditions in the dissertation were also extracted: qualitative and quantitative sameness of composition, physical and structural comparison of at least three test lots and three reference lots, comparison of release rate using in vitro release testing and in vitro permeation testing on excised human skin, method validation elements, good laboratory practice under 21 CFR Part 58, and retention and record-keeping of study samples (21 CFR 320.38, 320.63 and 320.36).5 The dissertation summaries could not be compared with the current guidance texts because the agency's guidance server was not reachable from the authors' environment (Section 2.8); they are therefore reported as recorded.

3. STATISTICAL ANALYSIS

No statistical analysis was performed, and no software was used for statistical testing. The study is a descriptive comparison of regulatory documents, so sample size (n) and probability (P) values do not apply, and no tabulated value carries a standard deviation.

4. RESULTS AND DISCUSSION

4.1. Results

4.1.1. Regulators and Legal Bases

Table 1 lists the regulator, legal basis, dossier format and bioequivalence framework for each jurisdiction. All six jurisdictions organise the dossier on the Common Technical Document and require evidence of bioequivalence to a reference product or an accepted waiver. They differ in the legal instrument, the language of submission and, for Russia, the level at which the rules are set, because registration follows Eurasian Economic Union rules.

Table 01: Regulators and legal bases for generic medicines in the United States and Brazil, Russia, India, China and South Africa

Jurisdiction	Regulator	Principal legal basis for generics	Dossier format and language	Bioequivalence framework
United States	FDA (CDER, Office of Generic Drugs)	FD&C Act; Hatch-Waxman Amendments; 21 CFR Part 314	eCTD; English	21 CFR Part 320; FDA product-specific guidances
Brazil	ANVISA	Law 6,360/1976 as amended by Law 9,787/1999; RDC 753/2022	CTD-based; Portuguese	Pharmaceutical equivalence plus bioequivalence against the reference medicine
Russia	Ministry of Health (federal expert institution evaluates; Roszdravnadzor enforces)	EAEU Rules of registration (EEC Council Decision 78/2016)	EAEU CTD-based; Russian	EAEU bioequivalence rules (EEC Council Decision 85/2016)
India	CDSCO, headed by the DCGI	Drugs and Cosmetics Act 1940 and Rules 1945; NDCT Rules 2019	CTD-based; English	NDCT Rules 2019, with ethics committee oversight of studies
China	NMPA (technical review by CDE)	Drug registration regulations; chemical drug acceptance guidelines of 2025	CTD-based; Chinese	Reference preparation lists published by the CDE
South Africa	SAHPRA	Medicines and Related Substances Act 101 of 1965, as amended	CTD-based; English	Full, abridged and reliance review routes

FDA, Food and Drug Administration; CDER, Center for Drug Evaluation and Research; FD&C Act, Federal Food, Drug, and Cosmetic Act; CFR, Code of Federal Regulations; ANVISA, Brazilian Health Regulatory Agency; RDC, Collegiate Board Resolution; EAEU, Eurasian Economic Union; EEC, Eurasian Economic Commission; CDSCO, Central Drugs Standard Control Organisation; DCGI, Drugs Controller General of India; NDCT, New Drugs and Clinical Trials; NMPA, National Medical Products Administration; CDE, Center for Drug Evaluation; SAHPRA, South African Health Products Regulatory Authority; CTD, Common Technical Document; eCTD, electronic CTD. Sources are listed in Section 2.3. Statistical values (n, P) are not applicable.

4.1.2. Review Structure of the United States Pathway

An application is first assessed for acceptability and completeness (Figure 2). An application that fails this check receives a refuse-to-file letter. Accepted applications proceed to parallel bioequivalence, chemistry and microbiology, and labelling reviews, and a plant inspection may be requested. If the bioequivalence review is not acceptable, a bioequivalence deficiency is issued, and if the chemistry, microbiology or labelling review is not acceptable the application is not approved in that cycle. If the pre-approval inspection is acceptable the application is approved; otherwise approval is deferred pending a satisfactory inspection.

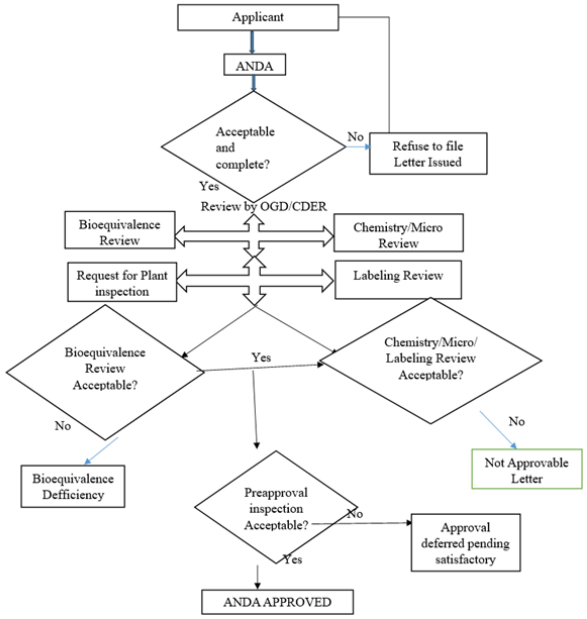


Figure 02: Review flow of an abbreviated new drug application. Redrawn from the authors' dissertation; the outcome labelled "not approvable letter" is issued as a complete response letter in current practice. OGD, Office of Generic Drugs; CDER, Center for Drug Evaluation and Research; ANDA, abbreviated new drug application.

The dossier is submitted in the electronic Common Technical Document format of five modules: administrative and prescribing information, summaries, quality, nonclinical reports and clinical reports. For an application for a generic product, Module 1 holds items such as the cover letter, forms, patent and exclusivity information, labelling comparison and environmental assessment or categorical exclusion, Module 3 holds the drug substance and drug product quality information, and Module 5 holds bioequivalence study reports. For fiscal year 2027, the application fee is US$375,684. The third authorisation of the user fee programme expires at the end of September 2027, and a performance goal of 10 months applies to standard original applications.

4.1.3. Procedural Comparison

Table 2 compares procedural features and the review durations reported in the earlier comparative study. These durations are nominal. Observed times can be much longer, as the average of 795 days reported for Brazil and the backlog inherited by the South African regulator show. The same compilation reports application fees of roughly US$1,000 to US$10,000 for the five comparator countries; these figures were not verified and should be confirmed with each authority.

Table 02: Procedural features and indicative review durations

Jurisdiction	Dossier basis	Indicative review duration	Notable current features
United States	eCTD, required for ANDAs	6-10 months	User-fee-funded review; patent certification and 180-day first-applicant exclusivity; tentative approval; complete response letter
Brazil	CTD-based, Portuguese	6-8 months	Generic requirements consolidated in RDC 753/2022; an average of 795 days is reported for 138 generics in 2013-2016
Russia	EAEU CTD-based, Russian	12-15 months	Unified EAEU rules since 1 January 2021; national certificates valid no later than 31 December 2025
India	CTD-based, English	6-12 months	NDCT Rules 2019; ethics committee oversight of bioequivalence studies; later applicants for an approved new drug rely on bioequivalen

			ce data
China	CTD-based, Chinese	6-8 months	Patent declaration through a listing platform; 2025 acceptance guidelines; CDE reference preparation lists
South Africa	CTD-based, English	8-12 months	Reliance and abridged routes; a backlog of about 16,000 applications was inherited in 2018

ANDA, abbreviated new drug application; eCTD, electronic Common Technical Document; CTD, Common Technical Document; EAEU, Eurasian Economic Union; NDCT, New Drugs and Clinical Trials; CDE, Center for Drug Evaluation. Durations are nominal figures from the earlier comparative study listed in Section 2.3 and were not independently verified. Statistical values (n, P) are not applicable.

4.1.4. Descriptions Superseded by Current Instruments

Table 3 sets statements from the earlier compilation beside the position found in November 2026. Differences arise in the names of regulators in China and South Africa, the registering authority and rules in Russia, the governing rules in India and Brazil, and the fee and outcome terminology in the United States.

Table 03: Statements in the earlier compilation compared with the position in November 2026

Statement in the earlier compilation	Position found in November 2026
United States: ANDA fee of US$240,582	ANDA fee of US$375,684 for fiscal year 2027 (1 October 2026 to 30 September 2027)
United States: outcome labelled "not approvable letter"	Deficiencies are communicated in a complete response letter
Brazil: Federal Law 6,360/1976 and earlier generic resolutions	Law 6,360/1976 as amended by Law 9,787/1999; RDC 753/2022 sets criteria and documentation for marketing authorisation of generic medicines
Russia: Roszdravnadzor grants registration through a national procedure	Ministry of Health registers under EAEU rules since 1 January 2021; Roszdravnadzor is the enforcement authority; national certificates ended no later than 31 December 2025
India: Schedule Y and Rule 122A of the 1945 Rules	New Drugs and Clinical Trials Rules, 2019
China: SFDA and CFDA; Drug Administration Law 2001 and Regulations 2002	NMPA, with the CDE as technical reviewer; the 2001 law has since been revised
South Africa: MCC; standard process of about 720 business days	SAHPRA since February 2018; reliance and abridged review routes; backlog clearance strategy

ANDA, abbreviated new drug application; EAEU, Eurasian Economic Union; SFDA, State Food and Drug Administration; CFDA, China Food and Drug Administration; NMPA, National Medical Products Administration; CDE, Center for Drug Evaluation; MCC, Medicines Control Council; SAHPRA, South African Health Products Regulatory Authority; RDC, Collegiate Board Resolution. Statistical values (n, P) are not applicable.

4.1.5. Antiviral Case Studies

Table 4 summarises the product-specific recommendations for the two antivirals. The acyclovir cream guidance offers an in vitro option based on formulation sameness, physicochemical comparison and release-rate comparison, or an in vivo clinical endpoint study. The oseltamivir capsule guidance offers a biowaiver or two pharmacokinetic studies, with fasting and fed conditions, and a waiver of in vivo testing for lower strengths under stated conditions.

Table 04: Product-specific bioequivalence recommendations for acyclovir topical cream and oseltamivir phosphate capsules

Feature	Acyclovir, topical cream	Oseltamivir phosphate, oral capsule
Recommended approaches	Two options: in vitro, or in vivo study with a clinical endpoint	Two options: biowaiver based on BCS, or two in vivo bioequivalence studies with pharmacokinetic endpoints
In vitro or waiver route	Test and reference products have the same qualitative (Q1) and quantitative (Q2) composition; at least three test batches and three reference lots, where available, show comparable physicochemical characteristics; an in vitro release	BCS Class III biowaiver, provided that the drug is highly soluble and dissolves quickly and that the test formulation matches the reference in quality and quantity of excipients

	test on at least one batch of each product shows the same release rate with an appropriately approved method	
In vivo route	Randomised, double-blind, parallel, three-arm (test, reference, placebo) study in immunocompetent adults with recurrent herpes labialis; a large sample is likely because the reference product shows modest efficacy	Single-dose, two-period, two-treatment crossover studies under fasting and fed conditions at the EQ 75 mg strength in subjects from the general population
Analytes and criterion	Not applicable for the in vitro option; clinical endpoint for the in vivo option	Oseltamivir and its active metabolite oseltamivir carboxylate in plasma; 90% confidence intervals for the parent drug; metabolite data presented to support similar therapeutic effect
Other strengths	Not specified in the source summary	In vivo waiver for EQ 30 mg and EQ 45 mg strengths when dissolution and proportional-similarity conditions are met
Dissolution	Not applicable	Method from the FDA dissolution methods database; 12 dosage units of test and reference for each strength

BCS, Biopharmaceutics Classification System; EQ, equivalent to; Q1, qualitative sameness; Q2, quantitative similarity. Summaries follow the guidance documents named in Section 2.7; consult current versions before use. Statistical values (n, P) are not applicable.

Case study 1 - acyclovir topical cream. Acyclovir is a nucleoside analogue used against herpes infections, and its cream is applied to the skin, where the drug acts locally. Because plasma concentrations do not reflect drug at the site of action, the guidance offers two options.13 The in vitro option requires three conditions. First, the test and reference products must be qualitatively (Q1) and quantitatively (Q2) the same, as defined in the agency's refuse-to-receive standards for abbreviated applications, which also makes them pharmaceutically equivalent for therapeutic equivalence evaluation. Second, they must be physically and structurally similar, shown by a comparative physicochemical characterisation of at least three lots of the test product and three lots of the reference product, as available; each lot is analysed separately and the work is done within a quality system that follows good laboratory practice (21 CFR Part 58). Third, they must show an equivalent rate of acyclovir release in an in vitro release test (IVRT) comparing at least one lot of each. The dissertation names the release test as run with a validated method; this article reads that as the IVRT.

The IVRT follows the compendial performance tests for semisolid products. The test and reference products are dosed alternately on successive diffusion cells, and their packaging is made to look alike so that analysts cannot tell them apart. Results of exploratory method development are submitted for review even when not generated under a validated method. The pivotal method must be validated, qualified or justified for the apparatus, membrane, receptor solution, receptor sampling, analytical method for receptor samples, environmental control, linearity and range, precision and reproducibility, recovery with mass balance and dose depletion, discrimination, sensitivity, specificity and selectivity, and robustness. The dissertation then describes an in vitro permeation test (IVPT) as a parallel, single-dose, multiple-replicate comparison of the cutaneous pharmacokinetics of acyclovir from the test and reference products on excised human skin with an intact barrier, mounted on a qualified diffusion cell system. Its validation covers apparatus, skin membrane, receptor solution and sampling, analytical method, environmental control, a pilot study, permeation profile and range, precision and reproducibility, recovery and mass balance, discrimination, robustness, and control of study procedures, with tight control of variables to exclude bias. Samples are retained, and records kept, under 21 CFR 320.38, 320.63 and 320.36.5

The in vivo option is a bioequivalence study with a clinical endpoint: a randomised, double-blind, parallel, three-arm study of the test product, the reference product and a placebo in healthy, immunocompetent adult men and non-pregnant, non-lactating women with recurrent herpes labialis (cold sores). Because the reference product shows modest efficacy, a relatively large number of subjects is expected. Acyclovir concentrations are measured only for the in vitro option, no dissolution method applies, and the basis of

the 90% confidence interval follows the option chosen. In the electronic dossier, a request to waive in vivo evidence goes in Module 1 (item 1.12.15), the comparative study reports in Module 5 (5.3.1.2) and the product comparison in Module 3.

Case study 2 - oseltamivir phosphate oral capsule. Oseltamivir phosphate is an oral neuraminidase inhibitor used against influenza, and the capsule acts systemically through its active metabolite, oseltamivir carboxylate.14 The guidance offers a biowaiver or two pharmacokinetic studies. Under option 1, a request to waive in vivo testing may be considered on a BCS Class III basis when the documentation shows high solubility and very rapid dissolution, and the test formulation is qualitatively the same and quantitatively similar to the reference, as set out in the harmonised guideline on biopharmaceutics classification system-based biowaivers;31 the agency decides on the request after it assesses the data in the application.

Under option 2, two single-dose, two-treatment, two-period crossover studies are run, one fasting and one fed, at the 75 mg (as base) strength in men and non-pregnant, non-lactating women from the general population. Oseltamivir and oseltamivir carboxylate are measured in plasma. Bioequivalence is judged on the 90% confidence intervals for the parent drug, while metabolite data are submitted as supportive evidence of comparable therapeutic outcome: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for the area under the curve (AUC) and maximum concentration (Cmax). In vivo testing of the 30 mg and 45 mg (as base) strengths may be waived when three conditions are met: acceptable bioequivalence studies at 75 mg, acceptable in vitro dissolution of all strengths, and proportionally similar formulations across strengths. The dissolution method is taken from the agency's dissolution methods database, comparative testing uses 12 dosage units of each strength of test and reference, and specifications are set during review of the application.

The two cases differ in what proves equivalence. For acyclovir cream, equivalence rests on formulation sameness, structural similarity and drug release or skin permeation, or on a clinical endpoint study that needs many subjects. For oseltamivir capsules, equivalence rests on plasma exposure of the parent drug under fasting and fed conditions, or on a biowaiver if the drug and formulation meet the stated criteria. A developer can therefore plan the evidence package before formulation work starts, for instance by matching the reference formulation (Q1 and Q2) when the in vitro route is wanted for a topical product.

4.2. DISCUSSION

4.2.1. Principal Findings

The main finding is that generic antiviral approval in the six jurisdictions rests on shared foundations (a dossier organised on the Common Technical Document and proof of bioequivalence to a reference product) while national instruments, languages and procedures remain distinct. The Common Technical Document was designed by the International Council for Harmonisation to simplify submission requirements across regions [30], and earlier comparative work reached a similar conclusion about the value of harmonised submission formats [8,11]. The present comparison confirms that the technical core of an antiviral generic dossier is largely transferable, whereas Module 1, language and legal instruments are not.

4.2.2. Differences That Shape Filing Strategy

Four differences stand out. First, patent linkage and exclusivity differ: the United States combines patent certification, 180-day exclusivity for first applicants and tentative approval under the Hatch-Waxman framework [3,4], while China now requires generic applicants to declare patent status through a listing platform [27]. Second, reliance on assessments by other regulators is explicit in South Africa, where full, abridged, verified, recognition and notification routes were formalised,28 and in India, where later applicants for an approved new drug are assessed on chemistry and bioequivalence data without repeating clinical trials.26 The United States abbreviated pathway instead relies on the regulator's own findings for the reference product [4]. Third, regional integration changes the unit of regulation: Russia now applies Union rules,22,23 and national certificates were valid only until the end of 2025,24 so a dossier built on older national requirements would need to be re-examined. Fourth, regulatory capacity affects real timelines. A 2023 study reports an average of 795 days for 138 generic approvals in Brazil in 2013-2016 and describes the South African backlog [29], and the South African regulator reports inheriting about 16,000 applications in 2018 [28]. Nominal durations quoted in comparative tables 11 should therefore be read as targets rather than expectations.

4.2.3. Product-Specific Expectations

The acyclovir and oseltamivir cases show that the evidence package depends on dosage form and site of action at least as much as on jurisdiction. For a locally acting topical product, plasma concentrations do not reflect the site of action, so the guidance relies on formulation sameness and release-rate comparison, or on a clinical endpoint study [13]. For a systemically acting oral capsule, equivalence rests on plasma pharmacokinetics under fasting and fed conditions or, when the drug and formulation meet stated criteria, on a biowaiver [14,31]. These designs follow the general bioequivalence principles of Part 320 of Title 21 of the Code of Federal Regulations.5 Applicants targeting several countries should check the expectations of each authority for the specific product instead of assuming that a design accepted by one regulator will be accepted unchanged by another; Russian bioequivalence studies, for example, follow Union rules [23].

4.2.4. Fees, Funding and Capacity

The fee for an application in the United States is US$375,684 in fiscal year 2027.18 It supports a review

programme with defined performance goals [17]. and the programme is due for reauthorisation after September 2027.19 The much lower fees reported for the comparator countries come from a 2022 compilation and may no longer apply [11]. The South African experience shows that limited capacity, not fee level alone, can produce long delays [29].

4.2.5. Limitations and Future Scope

This is a narrative review and the selection of sources was not exhaustive. Review durations and fees for the comparator countries come from a single earlier compilation [11]. Several current items were checked through secondary sources, including a law-firm bulletin and a consultancy summary [24, 27], and should be confirmed against the official texts. The recommendations in Table 04 reflect the guidance summaries available to the authors; product-specific guidances are revised, and the current versions should be consulted [13,14]. Batch-size, climatic-zone and stability-duration requirements are not tabulated because they vary by authority and change often; the harmonised stability guideline is a starting point.32 No regulator or industry representative was interviewed. Future work could extend the comparison to further regulators, verify durations against agency performance data, and track how reliance and Union-level pathways affect generic antiviral availability.

5. CONCLUSION

The aim of this study was to compare the abbreviated new drug application pathway of the United States with generic drug registration in Brazil, Russia, India, China and South Africa, using two antivirals to illustrate product-specific bioequivalence expectations. All six jurisdictions rely on a dossier organised on the Common Technical Document and on proof of bioequivalence, yet they differ in legal instruments, language, review structure, reliance on other regulators, patent linkage and real review times. Several descriptions in earlier compilations are superseded: the Chinese and South African regulators have new names, Russia applies Eurasian Economic Union rules, Brazil's generic requirements are consolidated in a 2022 resolution, India's 2019 rules replaced Schedule Y, and the United States fee and letter terminology have changed. The acyclovir and oseltamivir cases show that the bioequivalence design depends on dosage form and site of action, and that in vitro and biowaiver routes can replace clinical studies when strict criteria are met. Applicants should combine a harmonised core dossier with jurisdiction-specific modules and confirm current requirements with each authority at the time of filing. Future work should verify review durations against agency data and follow the effect of reliance and Union-level pathways on generic antiviral availability.

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9. CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

10. REFERENCES

1. De Clercq E, Li G. Approved antiviral drugs over the past 50 years. Clin Microbiol Rev. 2016 Jul;29(3):695-747.
2. Kausar S, Said Khan F, Ishaq Mujeeb Ur Rehman M, Akram M, Riaz M, Rasool G, et al. A review: mechanism of action of antiviral drugs. Int J Immunopathol Pharmacol. 2021 Mar;35:20587384211002621.
3. Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments). Pub. L. No. 98-417, 98 Stat. 1585 (1984).
4. U.S. Food and Drug Administration. Abbreviated New Drug Application (ANDA) [Internet]. Silver Spring (MD): FDA; [Accessed on 2026 Nov 10]. Available from: https://www.fda.gov/drugs/types-applications/abbreviated-new-drug-application-anda
5. Electronic Code of Federal Regulations. Title 21, Part 320: Bioavailability and bioequivalence requirements [Internet]. [Accessed on 2026 Nov 10]. Available from: https://www.ecfr.gov
6. Sravika S, Bhavana R, Sharmila V, Anusha S, Mounica NVN, Reddy DN, et al. A comprehensive study on regulatory requirements for development and filing of generic drugs globally. Pharma Innov. 2017 Apr 1;6(4 Pt C):153.
7. Handoo S, Arora V, Khera D, Nandi PK, Sahu SK. A comprehensive study on regulatory requirements for development and filing of generic drugs globally. Int J Pharm Investig. 2012 Jul;2(3):99.
8. Tejorani M, Bonthagarala B, Ramakrishna G, Nagabhushanam M. Comparative studies for filing and marketing authorisation of generic drugs in Europe, United States and India. Indo Am J Pharm Sci. 2021:165-73. doi:10.5281/zenodo.5225920
9. Kavitha M. A review on generic drugs registration procedure in USA & Canada. World J Pharm Res. 2017:452-63. doi:10.20959/wjpr20177-8722

10. Badjatya JK. Regulatory requirements and registration process of generic drugs in China. PharmaTutor. 2016 Feb 1;4(2):13-8.
11. Deore D, Patel P. Comparative overview of registration and approval process for generic drugs in BRICS countries. Int J Drug Regul Aff. 2022;10:40-50. doi:10.22270/ijdra.v10i1.509
12. Hasan MI, Shimu SA, Akther A, Jahan I, Hamiduzzaman M, Hasan AN. Development of generic drug products by pharmaceutical industries considering regulatory aspects: a review. J Biosci Med. 2021 Sep 30;9(10):23-39.
13. U.S. Food and Drug Administration. Product-specific guidance for acyclovir (topical cream) [Internet]. Silver Spring (MD): FDA; [Accessed on 2026 Nov 10]. Available from: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm
14. U.S. Food and Drug Administration. Product-specific guidance for oseltamivir phosphate (oral capsule) [Internet]. Silver Spring (MD): FDA; [Accessed on 2026 Nov 10]. Available from: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm
15. Grand View Research. Antiviral drugs market size, share & growth report, 2030 [Internet]. San Francisco: Grand View Research; [Accessed on 2026 Nov 10]. Available from: https://www.grandviewresearch.com
16. Electronic Code of Federal Regulations. Title 21, Part 314: Applications for FDA approval to market a new drug [Internet]. [Accessed on 2026 Nov 10]. Available from: https://www.ecfr.gov
17. U.S. Food and Drug Administration. GDUFA reauthorization performance goals and program enhancements, fiscal years 2023-2027 (GDUFA III commitment letter) [Internet]. Silver Spring (MD): FDA; [Accessed on 2026 Nov 10]. Available from: https://www.fda.gov/media/153631/download
18. U.S. Food and Drug Administration. Generic drug user fee rates for fiscal year 2027. Fed Regist [Internet]. 2026 Jul 30 [Accessed on 2026 Nov 10]; Doc. 2026-15343. Available from: https://www.federalregister.gov/documents/2026/07/30/2026-15343/generic-drug-user-fee-rates-for-fiscal-year-2027
19. U.S. Food and Drug Administration. Notice on reauthorization of the Generic Drug User Fee Amendments for fiscal years 2028 to 2032. Fed Regist [Internet]. 2026 [Accessed on 2026 Nov 10]; Doc. 2026-16353. Available from: https://public-inspection.federalregister.gov/2026-16353.pdf
20. Brazil. Lei n. 9.787 de 1999, que altera a Lei n. 6.360, de 23 de setembro de 1976, sobre medicamentos genericos [Law No. 9,787 of 1999 amending Law No. 6,360 of 23 September 1976 on generic medicines]. Brasilia: Presidencia da Republica.
21. Agencia Nacional de Vigilancia Sanitaria (Anvisa). Resolucao da Diretoria Colegiada RDC n. 753, de 28 de setembro de 2022. Diario Oficial da Uniao. 2022 Oct 5;(190) [Internet]. [Accessed on 2026 Nov 10]. Available from: https://www.gov.br/anvisa/en/rules-and-regulations/arquivos/rdc-753_2022.pdf
22. Eurasian Economic Commission Council. Decision No. 78 of 3 November 2016 on the Rules of registration and evaluation of medicines for medical use. Moscow: Eurasian Economic Commission; 2016.
23. Eurasian Economic Commission Council. Decision No. 85 of 3 November 2016 on the Rules for conducting bioequivalence studies of medicinal products within the Eurasian Economic Union. Moscow: Eurasian Economic Commission; 2016.
24. ALRUD. Head start to 2021 for the pharmaceutical industry in Russia [Internet]. Moscow: ALRUD; [Accessed on 2026 Nov 10]. Available from: https://alrud.com/publications/854
25. Ministry of Health and Family Welfare, Government of India. New Drugs and Clinical Trials Rules, 2019 (as amended) [Internet]. New Delhi: Central Drugs Standard Control Organisation; [Accessed on 2026 Nov 10]. Available from: https://cdsco.gov.in
26. Medical Dialogues. Unequal trials in new drug approvals: CDSCO seeks feedback for policy reform [Internet]. [Accessed on 2026 Nov 10]. Available from: https://medicaldialogues.in/amp/news/industry/pharma/cdsco/unequal-trials-in-new-drug-approvals-cdsco-seeks-feedback-for-policy-reform-156638
27. Cisema. NMPA issues new "Chemical Drug Registration Acceptance Review Guidelines" to standardize drug registration process [Internet]. 2025 Apr 9 [Accessed on 2026 Nov 10]. Available from: https://cisema.com/news/chemical-drug-registration-nmpa-guidelines
28. South African Health Products Regulatory Authority. Medical products backlog clearance strategy [Internet]. Pretoria: SAHPRA; [Accessed on 2026 Nov 10]. Available from: https://sahpra.org.za/backlog
29. Moeti L, Litedu M, Joubert J. Regulatory registration timelines of generic medicines in South Africa: assessment of the performance of SAHPRA between 2011 and 2022. J Pharm Policy Pract. 2023 Mar. PMCID: PMC9983237.
30. International Council for Harmonisation. M4: The Common Technical Document [Internet]. Geneva: ICH; [Accessed on 2026 Nov 10]. Available from: https://www.ich.org
31. International Council for Harmonisation. M9: Biopharmaceutics classification system-based biowaivers. ICH harmonised guideline [Internet]. Geneva: ICH; 2019 [Accessed on 2026 Nov 10]. Available from: https://www.ich.org
32. International Council for Harmonisation. Q1A(R2): Stability testing of new drug substances and products. ICH harmonised tripartite guideline

[Internet]. Geneva: ICH; [Accessed on 2026 Nov 10]. Available from: https://www.ich.org