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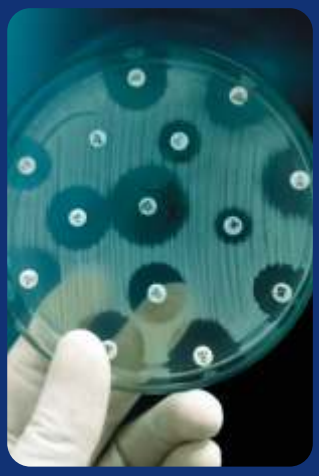


DRUG REGULATORY APPROVALS AND OPPORTUNITIES FOR ANTIMICROBIAL INNOVATION

PERSPECTIVES FROM BRAZIL, INDIA AND SOUTH AFRICA

July 2022

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The findings and conclusions contained within are those of the authors and do not necessarily reflect the positions or policies of OHT or AMRIA.

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Related research and additional information on access to antibiotics and antibiotic use and resistance are available at onehealthtrust.org

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Foreword

Much has been written about the growing morbidity and mortality caused by antibiotic resistance, especially in low- and middle-income countries. The problem is frequently blamed on the overuse of antibiotics and appropriately so, but insufficient attention has been given to the underlying problem of lack of access to antibiotics. When patients lack access to antibiotics that work in place of those to which resistance has developed, they are more likely to suffer the consequences of AMR.

A major reason for lack of access is that antibiotics are not registered widely. A study published by the One Health Trust with collaborators at the Norwegian Institute of Public Health found that of 25 new antibiotics introduced between 1999 and 2014, only 12 had registered sales in more than 10 countries . Nine antibiotics had limited geographic availability with registered sales in five countries or less. Simply developing new antibiotics without registering them in all countries where patients are in need wastes the significant resources that go into new antibiotic development and denies companies access to key markets that could make new antibiotic development more financially rewarding than it currently is.

This report describes the regulatory barriers to getting new antibiotics registered in more countries, with specific insights from Brazil, India, and South Africa. Antibiotics are different from other drugs in many respects, including the need for the periodic introduction of new drugs to replace ones to which resistance has developed and the complexity of trials to identify drugs that are effective against drug-resistant pathogens. Appropriately, this report identifies the acknowledgment of AMR in regulatory frameworks for drug approvals as an opportunity to improve the wider availability of new antibiotics.

Much remains to be done to improve how we use antibiotics globally and to reduce the need for antibiotics through vaccines, water and sanitation, and infection prevention. But these will not be sufficient. The growing burden of AMR will need to be addressed with new antibiotics. Unless we significantly rethink and revise current processes for regulatory approvals, the burden of AMR will keep increasing. The insights in this report could help shed light on what we need to do to make more new antibiotics accessible to more patients in need, regardless of where they live.

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[1]Källberg, C. et al. Introduction and geographic availability of new antibiotics approved between 1999 and 2014. PLoS ONE 13, e0205166 (2018).

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Abbreviations

2019-CTRules	New Drugs and Clinical Trials Rules–2019 (India)
AMA	African Medicines Agency
AMR	antimicrobial resistance
AMRH	African Medicines Regulatory Harmonization
ANVISA	Agência Nacional de Vigilância Sanitária (Brazil)
AVAREF	African Vaccine Regulatory Forum
AWaRe	Access, Watch, and Reserve (classification of antibiotics)
CDSCO	Central Drugs Standard Control Organization (India)
CTA	clinical trial application
DCGI	Drug Controller General of India
EMA	European Medicines Agency
GAIN	Generating Antibiotic Incentives Now (U.S. act)
GAP	Global Action Plan
HIV	human immunodeficiency virus
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMRA	International Coalition of Medicines Regulatory Authorities
MCC	Medicines Control Council
MDR	multidrug-resistant
MRSA	methicillin-resistant*Staphylococcus aureus*
NAS	new active substances
NCE	new chemical entity
NRA	national regulatory authority
PIC/S	Pharmaceutical Inspection Cooperation Scheme (South Africa)
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
R&D	research and development
REPAIR	Replenishing and Enabling the Pipeline for Anti-Infective Resistance (U.S. act)
SAHPRA	South African Health Products Regulatory Authority
SEC	subject expert committee (India)
TB	tuberculosis
U.S. FDA	U.S. Food and Drug Administration
WHO	World Health Organization

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Executive Summary

Antimicrobial resistance (AMR), a global health and development threat, is regarded by public health experts as a "silent pandemic" that is often overlooked because of competing public health emergencies[1]. Globally, an estimated 4.95 million deaths were associated with antimicrobial-resistant bacterial infections, and 1.27 million deaths were directly attributable to such infections in 2019[2]. The appropriate use of existing antibiotics and the development of new antibiotics targeting drug-resistant infections can slow the emergence, spread, and consequences of AMR; however, antibiotic research and development (R&D) has not responded to the urgent need for new antibiotics[3]. A lack of investment in antibiotic R&D explains the failing clinical and preclinical antibiotic pipelines: antibiotics are costly to produce, and their low prices and restricted use do not make their development economical[4]. Although financial incentives and market reforms are deemed critical for sustainable progress, addressing regulatory hurdles to accelerate approval of new antibiotics can also help their development and improve access in emerging markets.

This analysis of the regulatory framework for antibiotic approval in three middle-income countries—South Africa, Brazil, and India—highlights the importance of explicitly recognizing new antimicrobials targeting serious or life-threatening infections as a critical unmet medical need and formalizing their inclusion in regulatory frameworks for accelerated drug approval. The national regulatory authorities (NRAs) in the three countries have taken steps to expedite the registration of medicines, and in some instances, flexibility has been granted in clinical trial requirements for drugs targeting unmet public health needs; however, antimicrobials and multidrug-resistant infections are not explicitly included in the list of eligible drugs and indications.

Accelerated drug approvals often involve risk-based approaches or reliance on other countries' regulatory assessments. As a result, increasing collaboration and harmonization between health authorities are necessary for global coordination in the fight against AMR. With NRAs from high-income countries working toward harmonization and alignment, the inclusion of less-developed NRAs in bilateral and multilateral collaborations could provide valuable perspectives for regulatory innovations to address AMR at a global level. The COVID-19 pandemic has demonstrated what can be achieved through collaboration and harmonization when countries face global public health emergencies.

Recommendations to accelerate the approval of antibiotics in emerging markets

- Create a specific category for antimicrobials that target serious and life-threatening infections within the regulatory framework provided for accelerated approval pathways.
- Leverage existing programs for expedited approval for drugs targeting TB, HIV, and COVID-19 to accelerate the approval of antimicrobials targeting serious and life-threatening infections, such as multidrug-resistant infections.
- Increase regulatory authorities' capacities to deal with the complexity of AMR and novel clinical trials.
- Increase regulatory harmonization to facilitate the adoption of reliance pathways for accelerated approval of antimicrobials.

Overview

This report describes the current climate for antimicrobial innovation. It discusses regulatory challenges and opportunities for the approval of new antibiotics in three emerging markets: South Africa, Brazil, and India. The report is informed by reviews and analyses of several sources, including organizational reports, peer-reviewed literature, and press releases. Semistructured interviews with experts from international organizations and the scientific and regulatory ecosystem in the three countries were conducted between November 2021 and February 2022 to obtain global and national perspectives on the regulatory landscape for antibiotics.

Introduction

The global landscape for antibiotic research and development

An analysis of the current state of antibiotic development finds failing markets: the cost of drug development is high, the clinical uptake of new drugs is slow, and the number of target infections is insufficient to support existing drugs economically[4]. The World Health Organization (WHO) created the AWaRe (Access, Watch, and Reserve) classification in 2017 to promote the appropriate use of antibiotics and slow the emergence of antimicrobial resistance (AMR)[5]. However, for new antibiotics placed in the restricted category, this premise challenges their development from an economic perspective.

Despite some improvements since 2013 in the antibiotic development pipeline, pharmaceutical research and development (R&D) has not responded to the growing demand for new antibiotics[6]. Only three new classes of antibiotics against Gram-positive bacteria have been approved in the past two decades; the last new class of antibiotics against Gram-negative pathogens (fluoroquinolones) became available for clinical use in the 1960s[3]. A 2021 WHO report on the clinical antibacterial pipeline highlights the unmet need for antibiotics against Gram-negative bacteria; among 26 traditional antibacterial agents against WHO priority pathogens in the clinical pipeline, only two were active against multidrug-resistant (MDR) Gram-negative bacteria[7].

A lack of investment in antibiotic R&D is responsible for anemic clinical and preclinical pipelines for new antibiotics[8]. However, funding alone may represent only a short-term solution that does not obviate the need for additional market reforms[4].

Incentives for new antibiotic development

Innovative economic models that serve as incentives for developing new antibiotics fall into two categories. Push incentives consist of grants, subsidies, or tax incentives to lower the costs related to antibiotic R&D[9]. Examples include global initiatives, such as the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), the Biomedical Advanced Research and Development Authority's Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), the Global Antibiotic Research and Development Partnership (GARDP), The Replenishing and Enabling the Pipeline for Anti-Infective Resistance (REPAIR) Impact Fund, and the European Union's New Drugs for Bad Bugs (ND4BB) and Innovative Medicines Initiative (IMI). Pull incentives consist of economic models that provide rewards or known returns on the investment, such as advance market commitments, exclusivity or patent extensions, and market entry rewards that are partially or fully delinked (from unit sales)[9–11]. For example, the U.S. Generating Antibiotic Incentives Now (GAIN) Act was designed to promote the development of antibacterial and antifungal drugs to treat serious or life-threatening infections by extending market exclusivity for licensed products for an additional five years[12]. Although the GAIN act generated momentum for the approval of novel antibiotics, it has proven to be of limited impact due to the economic challenges of antibiotics [13].

Some European countries and the United States are exploring other pull incentives to tackle AMR. Prominent examples include delinked, subscription-style incentives, such as the U.K. pilot program created in 2019 by the National Health Service (NHS) England[14] and the Pioneering Antibiotic Subscriptions to End Upsurging Resistance (PASTEUR) Act in the United States[15]. As of April 2022, NHS England has begun commercial discussions with two drug manufacturers on subscription-style payments for the procurement of drugs against severe Gram-negative bacterial infections: cefiderocol (Fetcroja; Shionogi) and ceftazidime with avibactam (Zavicefta; Pfizer). In this context, subscription-style payments would guarantee the pharmaceutical companies a fixed annual fee for use of these medicines, regardless of the number of prescriptions issued[16].

National policymakers and antibiotic resistance experts have expressed support for antibiotic incentives, especially multinational ones; however, uncertainties about the incentives' suitability and cost remain[17]. Few countries are using innovative incentives to promote R&D for new antimicrobials, and endorsement for mechanisms to support AMR innovation requires a clear demonstration and communication of the public health burden and better public understanding of the challenges of bringing new antibiotics to patients.[10,17,18]

Programs for regulatory approval of antibiotics

There have been discussions about accelerating the licensure of new antibiotics by addressing regulatory hurdles. For example, the U.S. Food and Drug Administration (U.S. FDA) outlines specific strategies to address AMR through various programs. The Qualified Infectious Disease Product Designation scheme, introduced in 2012 in the GAIN Act, can facilitate priority review and fast-track designation for a "qualified infectious disease product," defined as "an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections, including those caused by an antibacterial or antifungal resistant pathogen."[19] The European Medicines Agency (EMA) provides specific guidelines for evaluating products to treat bacterial infections; these guidelines include flexibility on the data package to demonstrate clinical safety and efficacy for products against MDR organisms with few therapeutic options[20,21]. In 2009, AMR experts from U.S. and European Union government agencies created the Transatlantic Taskforce on Antimicrobial Resistance to address AMR in human and animal health; as of 2021, Canada, Norway, and the United Kingdom have joined this collaboration[22]. Since 2016, EMA, U.S. FDA, and Japan Pharmaceuticals and Medical Devices Agency (PMDA) have created a tripartite platform for alignment on primary endpoints, primary analysis populations, and noninferiority margins in antibiotic clinical trials[23].

In low- and middle-income countries, research indicates that administrative and technical barriers—rigid and lengthy regulatory pathways, multilayered decision-making processes, limited human and financial resources, and competency and knowledge gaps on new, complex products—prevent timely drug approvals [24]. Delays are compounded by the lack of regulatory harmonization between countries and inefficient adoption of reliance, leading to duplication of work and increased costs. Regulatory harmonization at the regional level through collaborative work and data sharing could reduce the time required for drug approval in countries with low national regulatory resources[25]. For example, the WHO's Prequalification of Medicines Programme, which assesses product safety, efficacy, and quality, has been referred to as the "quiet revolution" in global public health because it is accelerating access to good-quality drugs, including antibiotics, in countries with limited regulatory capacity[26]. The International Coalition of Medicines Regulatory Authorities (ICMRA), in which South Africa, Brazil, and India participate, is supporting the WHO efforts by promoting regulatory cooperation for the development and commercialization of products that mitigate AMR[27].

South Africa

Background

In the most comprehensive assessment of the global AMR burden to date, statistical modeling estimates that sub-Saharan Africa carries the largest AMR burden; whereas death rates associated with or directly attributed to AMR were estimated to be 64.0 and 16.4 per 100,000 globally, they were as high as 98.9 and 23.7 per 100,000, respectively, in sub-Saharan Africa[2]. These estimates place AMR as a leading cause of death from an infection ahead of HIV and malaria[1,2].

Data from the South African 2018 national surveillance report indicate the emergence of resistance to last-resort antibiotics. Between 2012 and 2017, Klebsiella pneumoniae, the most frequently isolated pathogen in blood samples, showed consistent resistance levels to third-generation cephalosporins (63–70%) and emerging resistance to carbapenems (2–8%)[28]. Furthermore, carbapenem resistance was high (81%) in Acinetobacter baumannii isolates across the country. The only remaining treatment option, colistin, is not registered in South Africa but can be obtained on request; an initial authorization by designated doctors at hospitals is followed by an application to the South African Health Products Regulatory Authority (SAHPRA) [29]. Molecular epidemiology data suggest that emerging resistance is not limited to humans and can be found among intensively produced livestock[30,31]. Moreover, global maps of AMR in livestock, assessed through point prevalence surveys, indicate resistance hotspots in South Africa[32].

The Antimicrobial Resistance National Strategic Framework 2014–2024 in South Africa provides a comprehensive one-health framework to address emerging resistance[33]. However, there are gaps in information on budgets, funding, and progress reports as indicators of the implementation of the national action plan on AMR[34]. South Africa is currently enrolled in the WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS-AMR), with 737 surveillance sites participating in the national surveillance system as of 2020[35].

The National Regulatory Authority in South Africa

SAHPRA, the NRA in South Africa, replaced the Medicines Control Council (MCC) and the Directorate of Radiation Control in 2018[36]. SAHPRA's mandate is to ensure efficient, effective, and ethical assessment and registration of medicines and medical devices that meet defined standards of quality, safety, efficacy, and performance through various activities, including licensing, inspection, law enforcement operations, laboratory analysis of biological products, postmarket surveillance and vigilance, and advertising[37]. SAHPRA oversees the conduct of clinical trials for both non-registered medicines and new indications of registered drugs in South Africa and employs the guidelines of the International Council on Harmonisation (ICH) on "Technical Requirements for Registration of Pharmaceuticals for Human Use" and the guidelines for "Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa 2019" to approve and regulate clinical trials[38].

South Africa is an ICH observer and has partnered with other African countries in the ZaZiBoNa Collaborative Review Procedure for Medicines Registration and the Southern African Development Community Pharmaceutical Programme[39]. Additionally, South Africa is aligned with and relies on the WHO's prequalification and emergency use listings and is a member of ICMRA and the Pharmaceutical Inspection Co-operation Scheme (PIC/S)[40]. Although South Africa has yet to sign the treaty to join the African Medicines Agency (AMA), South African regulatory experts contributed to drafting the treaty and sent a recommendation for ratification to the South African government . South African participation in the AMA could improve NRAs across Africa; AMA's mission is to provide targeted resources for making evidence-based scientific regulatory decisions and allow for technical backup and work-sharing among NRAs[41]. As of November 2021, SAHPRA was undergoing an assessment according to the WHO Global Benchmarking Tool for evaluation of NRAs and was anticipated to receive an assessment of performance at maturity level 3 . In this context, a regulatory authority performing at maturity levels 3 or 4 is eligible to qualify as a WHO-Listed Authority [42].

AMR is notably absent from SAHPRA's strategic plan for 2020–2024. The plan mentions strategic initiatives to create collaborative structures for introducing new medicines into pilot programs to address the high disease burden from human immunodeficiency virus (HIV), tuberculosis (TB), and cancer[43]. However, emerging evidence on the AMR burden globally and in sub-Saharan Africa warrants that AMR is also recognized under the public health emergency lens as a significant unmet need.

Medicine registration

SAHPRA's review process for medicine registration has improved since its transition from the MCC in 2018 [44]. In 2019, SAHPRA announced its Backlog Project strategy with the objective of clearing 16,000 applications inherited from the MCC [44]. The application review process comprises four models: full review, abridged review, verified review, and recognition review [45]. A full review consists of a complete assessment of quality, preclinical, and clinical data for medicines that have not been reviewed or approved by an NRA recognized by SAHPRA[45]. The abridged, verified, and recognition reviews represent risk-based approaches that rely on external assessments. In an abridged review, SAHPRA uses the evaluation report from another recognized NRA to guide the evaluation of a medicine that has been reviewed or approved by the NRA in question[45]. The verification review applies to a drug that has been approved by at least two recognized NRAs; in this instance, the product is validated for conformance to the authorized product specification[45]. Finally, the recognition review is applicable for evaluating dossiers for generic medicines approved by at least one recognized NRA; these medicines should correspond to the dosage form and strength of the reference product registered by SAHPRA[46].

SAHPRA recognizes assessment decisions from several high-income countries and multilateral regulatory organizations, including the PMDA, Health Canada, U.S. FDA, EMA, Therapeutic Goods Administration Australia, Swiss Agency for Therapeutic Products, and the WHO. In addition, SAHPRA recognizes decisions from regional organizations such as the Southern African Development Community Medicines Regulatory Harmonization initiative through the ZaZiBoNa Collaborative Review Procedure for Medicines Registration.

The adoption of reliance pathways has reduced review timeframes, thereby accelerating the assessment of new chemical entities (NCEs) and generic product applications for market authorization in South Africa[47]. Under SAHPRA's predecessor, the MCC, the median approval time for full reviews for registration of new active substances (NASs) ranged from 1,218 days (42 NASs) in 2015 to 2,124 days (15 NASs) in 2018[48]. Median approval times for NASs were reduced by 68% in 2020, compared with the 2018 median[46]. In 2020–2021, all 72 NCE

registered applications were processed within 590 days[49].

The *Backlog Project* strategy from 2019 included prioritizing the review of applications from "therapeutic areas with high unmet need" such as TB, HIV, and oncology [44]. In February 2022 SAHPRA formally introduced the Priority Review Pathway for new medicines and variations that address an unmet clinical need in the South African market; are superior in safety or efficacy to existing treatment options; target life-threatening conditions; address public health emergencies, or are intended for Orphan diseases [50]. Following a successful application for eligibility for this pathway, the Priority Review Pathway makes provision for a reduced time frame for assessment and registration of the drug. The Priority Review Pathway for an application is associated with a fee that SAHPRA intends to communicate in the future[50].

In its 2020–2021 annual report, SAHPRA cites a lack of human resources and heavy reliance on external reviewers as challenges to its improved review processes[49]. SAHPRA received help in reducing the backlog through project management, development of guidelines, and recruitment of external evaluators[44,49;] through an in-principle agreement to support SAHPRA's Backlog Reduction Project, the Bill & Melinda Gates Foundation donated USD2.84 million in 2019–2020 and USD1.19 million in 2020–2021[49]. Additionally, the National Department of Health and the U.S. Centers for Disease Control and Prevention provided USD1.69 million for the Backlog Reduction Project, to expedite the assessment of applications related to HIV and TB drugs[49]. SAHPRA is expected to receive additional donor support in the years to come .

As of December 2020, the costs associated with an application for registration of NCEs (first strength, first dosage) and generic products with clinical data were USD6,934 and USD5,246, respectively, whereas fees associated with the authorization of use of unregistered medicines in clinical trials ranged from USD674 for postgraduate studies to USD1,898 and USD2,021 for bioequivalence and safety and efficacy studies, respectively[51].

Lessons from the COVID-19 pandemic

The COVID-19 pandemic has highlighted regulators' ability to mitigate a public health emergency. SAHPRA has continuously updated information on adaptations to address medicine shortages, information on the conduct of clinical trials under pandemic conditions, and expedited reviews of applications related to COVID-19 vaccines and treatment[52,53]. Additionally, SAHPRA transitioned to digital platforms and implemented a file transfer protocol that reduced the times for receipt and allocation of dossiers[49] . The pandemic led to expedited assessments of clinical trial applications related to COVID-19 interventions; 96% (194 out of 203) of finalized human clinical trial applications were processed within 120 working days[49]. Furthermore, the pandemic significantly affected regulatory harmonization; for example, the Africa Regulatory Taskforce was established by the Africa Centres for Disease Control and Prevention, the African Medicines Regulatory Harmonization (AMRH) initiative, and the WHO African Vaccine Regulatory Forum (AVAREF) to support the regulatory framework for COVID-19 vaccines in Africa. South Africa, a member of AMRH and AVAREF, adopted expedited vaccine approval pathways for COVID-19 vaccines, especially for those with WHO emergency and prequalification listings[54,55].

[1] Information provided by key informant

[2] According to the WHO Global Benchmarking evaluation scale (1-4), level 1 indicates existence of some elements of regulatory system and 4 indicates operating at advanced level of performance and continuous improvement.

[3] Information provided by key informant

Opportunities for antimicrobial innovation

Best practices

- From the regulatory perspective, SAHPRA has taken significant steps to improve its review processes to reflect global best practices; the adoption of reliance pathways has reduced the time needed to process applications for the registration of medicines.
- South Africa has established collaborations with international organizations to leverage assessments and reduce duplication of work.
- Experience with rapid approval of clinical trials for COVID-19 vaccines has further developed clinical trial capabilities in South Africa.

Recommendations

- Include antimicrobials targeting serious or life-threatening infections in existing programs that expedite approval for drugs targeting TB, HIV, and COVID-19 vaccines.
- Mobilize donor support to accelerate the processing of applications for antimicrobials targeting serious or life-threatening infections of public health relevance in South Africa.

Brazil

Background

AMR is a public health threat in Brazil. Estimates of the global AMR burden indicate that in 2019, 63 and 15 deaths per 100,000 were associated with or directly attributed to AMR, respectively, in tropical Latin America (Brazil and Paraguay). These rates are similar to global estimates of 64.0 and 16.4 deaths per 100,000, respectively[2].

In 2011, high rates of carbapenem-resistant Enterobacterales were reported in different states across Brazil; methicillin-resistant Staphylococcus aureus (MRSA) rates were as high as 60% in 2011 and were related to an endemic Brazilian clone[56]. In 2019, the prevalence of carbapenem-resistant Klebsiella pneumoniae and Acinetobacter baumannii in hospital-acquired infections was estimated to be 39% and 81%, respectively[57]. The first law that prohibited the selling of certain antimicrobials without prescription was endorsed in late 2010, resulting in a reduction in the units of antimicrobials sold between 2007 and 2013[58–60]. However antibiotic sales increased again by 18% between 2016 and 2018 because of non-prescription sales[61,62].

To tackle the AMR problem, Brazil developed a national action plan on AMR for 2018–2022 based on the five pillars of the WHO Global Action Plan (GAP) on AMR, launched in 2015[63]. In addition, in 2017, the Brazilian NRA, Agência Nacional de Vigilância Sanitária (ANVISA), developed a national plan for AMR prevention and control in health services that describes national strategies to detect and mitigate healthcare-associated infections and antimicrobial resistance[64]. Two technical committees advise ANVISA on AMR surveillance and rational use, the Technical Chamber on Antimicrobial Resistance in Health Services and the Technical Committee of Rational Antimicrobial Use and Antimicrobial Resistance[64]. Brazil is currently enrolled in GLASS-AMR, with 71 surveillance sites participating in the national surveillance system[35].

National Regulatory Authority in Brazil

ANVISA was created in 1999 and is responsible for evaluating the quality, efficacy, and safety of medicines or health products for marketing authorization. ANVISA coordinates the Brazilian Health Regulatory System (Sistema Nacional de Vigilância Sanitária), which is part of the National Health System (Sistema Único de Saúde). ANVISA coordinates its activities with but is independent of the Ministry of Health[65]. Before being added to the health system, drugs approved by ANVISA are reviewed by the National Committee for Technology Incorporation (known as CONITEC) for effectiveness, superiority to existing medicines, and cost, among other criteria[66].

ANVISA has made progress toward international harmonization with other regulatory agencies and is now a member of ICH, ICMRA, the Pan American Network for Drug Regulatory Harmonization, and as of January 2021, PIC/S[67]. Based on an assessment of ANVISA by the Pan American Health Organization, Brazil had one of the most comprehensive legal and organizational regulatory frameworks in the Americas[68].

Medicine registration

All products that claim therapeutic effects are considered medical drugs and must be registered with ANVISA for manufacturing and sale. As an ICH member since 2016, ANVISA has been working to align regulatory requirements and guidelines (also called "Resolutions") with ICH guidelines; however, the higher level of detail in these resolutions has been cited for complicating the adoption of risk-based approaches[65,68]. A study assessing regulatory review timelines for ANVISA between 2013 and 2016 showed that the median approval time for 138 applications was 795 days[69]. Presubmission meetings in the early stages of the dossier preparation could further accelerate the assessment of applications [4]. Although Brazil has no accelerated pathways specific to the approval of antibiotics, applications can be made to ANVISA to expedite assessment through pathways that support innovation and address unmet health needs[5].

One option is a priority review pathway[70,71] established to allow for the rapid approval of products relevant to public health, including drugs for children, drugs for emerging or neglected diseases, vaccines for the national immunization program, new or innovative drugs manufactured in Brazil, and the first generic[72]. Compared with the usual pathway, the priority pathway timeline is significantly shorter for authorization requests (120 days vs. 365 days), postapproval changes (60 days vs. 180 days), and clinical trial authorization (45 days vs. 180 days)[66].

A second option accelerates the approval pathway for drugs targeting rare diseases[71,73]. Because of these two resolutions, applications for clinical trials related to rare, neglected, emerging, or re-emerging diseases and trials exclusively for pediatric and adolescent populations were the two most prioritized application categories by ANVISA in 2017 [66].

As a third option, in 2018, ANVISA launched a reliance pilot project, which is intended to be an abridged pathway for the approval of new biologics[71]. The abridged pathway involves an independent review of the dossier (registration, variations, postapproval changes) in the local context without reassessing scientific supporting data reviewed and accepted by U.S. FDA and EMA[69]. In 2019, this reliance mechanism was extended to synthetics and semi-synthetics [74]. Although these pathways represent an important step toward the adoption of reliance pathways, challenges remain regarding their effective implementation: advantages provided by the pathway are not clearly defined, and requirements for assessment reports from both EMA and FDA can lead to considerable delays, making them less attractive or less feasible [71].

Depending on the product category, ANVISA charges USD2,600 for the registration of a generic drug and USD34,980 for a new drug. Before 2018, more than 80% of innovative drug product requests were related to new concentrations or dosage forms[72].

[4] Information provided by key informant

[5] Information provided by key informant

Lessons from the COVID-19 pandemic

Like many NRAs worldwide, ANVISA adopted several emergency measures during the COVID-19 pandemic, including creating a designated committee to review clinical trial applications in 72 hours. Other measures aimed at regulating access to certain medicines comprised compassionate use authorizations, market control, and reliance mechanisms for good manufacturing practice inspections[68].

In response to the COVID-19 pandemic, ANVISA published a new resolution, which provides an accelerated pathway for drugs or biological products with the potential to reduce patient hospitalizations and health burden, such as drugs used to prevent or treat COVID-19 or manage associated diseases[75]. This regulation applies to new drug applications, biologics license applications, and postapproval changes. Under provisions provided by this pathway, manufacturing sites were replaced or new manufacturing sites were added to avoid antibiotic shortages during the COVID-19 pandemic. Furthermore, through another resolution, ANVISA included two antibiotics (polymyxin B and sulfamethoxazole-trimethoprim) in the list of drugs authorized for extraordinary and temporary importation by both private and public health facilities as part of the emergency measures to mitigate the pandemic[76].

During the pandemic, the system demonstrated that it could respond under stress to public health emergencies. For COVID-19 vaccine trials, a reallocation of human resources allowed ANVISA to conduct a rapid analysis of data sent by study centers, proving that strengthening the existing system through financial and human resources could help accelerate regulatory processes in emergency conditions[6].

Opportunities for antimicrobial innovation

Best practices

- ANVISA has implemented strategies to reduce its application backlog, including restructuring the review process, teleworking, and recruiting more evaluators.
- ANVISA has created priority pathways for drugs targeting public health needs and implemented a reliance pilot project for registration and postapproval changes for biological products registered by U.S. FDA and EMA.

Recommendations

- Create a specific category for antimicrobials targeting serious or life-threatening infections within the regulatory framework of accelerated approval pathways.
- Use experience from the COVID-19 pandemic to increase the adoption of risk-based approaches for drug approvals.
- Ensure alignment with academia and medical practices to obtain a better understanding of the value of new therapeutic drugs for complex health issues like AMR.

[6] Information provided by key informant

India

Background

India has one of the highest burdens of drug-resistant pathogens globally, including the highest burden of MDR TB[77]. Recent estimates indicate that in South Asia in 2019, 76.8 deaths per 100,000 were associated with AMR, and 21.5 deaths per 100,000 were directly attributed to AMR—higher than the global estimates of 64.0 and 16.4 deaths per 100,000, respectively[2]. In India, more than 58,000 neonatal deaths a year may be attributable to two common resistant organisms: extended-spectrum beta-lactamase producers and MRSA[78]. The global trend of heightened antibiotic resistance among Gram-negative bacteria is also seen in India. Within a few years, MDR patterns have transitioned to pan-drug resistance[79]. As of 2017, national AMR surveillance data showed that A. baumannii isolates were resistant to all antibiotics except colistin[80]. Recent estimates suggest a very high level of resistance to the Watch antibiotics in the WHO AWaRe category. In 2017, carbapenem (meropenem) resistance rates among A. baumannii, Klebsiella spp., and P. aeruginosa isolates were 73%, 59%, and 30%, respectively; the cefotaxime resistance rate among E. coli isolates was 77%; and ciprofloxacin resistance in Salmonella spp. (S. typhi and S. paratyphi) was 39%[80,81].

India's national action plan on AMR, established in 2017, details a five-year program consisting of six strategic priorities in line with the GAP on AMR. The sixth strategic objective aims to strengthen India's leadership on AMR by promoting collaborations at the international, national, and subnational levels. India is currently enrolled GLASS-AMR and has been contributing AMR data from the National Centre for Disease Control, Indian Council for Medical Research, and Gonococcal AMR Surveillance Programme networks[35]. As of 2020, 17 surveillance sites participate in the national surveillance system[35].

National Regulatory Authority in India

The Central Drugs Standard Control Organization (CDSCO), India's apex NRA, carries the responsibilities allotted to the Central Government by the Drugs and Cosmetics Act–1940. The affiliated institutions under the governance of CDSCO are listed in Table 1. The food and drug administrations are the regulatory authorities at the state level; licensing authorities represent regulatory authorities for the Union Territories. Regarding the Drugs and Cosmetics Act–1940, there is dual regulatory control, including the central and the state governments. It is the responsibility of these regulatory entities to ensure high-quality drug supply, market monitoring, and the rights, safety, and well-being of clinical trial participants. Additionally, several regulatory entities oversee drug production, preclinical and clinical trials, and drug marketing and pricing.

Within CDSCO, the Drug Controller General of India (DCGI) regulates pharmaceutical products and medical devices. The Drug Technical Advisory Board and the Drug Consultative Committee advise the DCGI. There are 25 subject expert committees (SECs) constituted by the Ministry of Health and Family Welfare, of which two committees (SEC Antiviral and SEC Antimicrobial) oversee applications on novel antimicrobials[82]. The Central Licensing Approval Authority is responsible for licensing and classifying medical devices, setting and enforcing safety

standards, performing postmarket surveillance, issuing warnings, and recalling pharmaceutical products for adverse events.

CDSCO and the state drug regulatory authorities have a range of jurisdictions over drug regulation but have limited interaction among themselves, which hinders their coordination[83]. Furthermore, strict regulatory requirements and a lack of clarity on regulations represent significant barriers to conducting clinical trials in India[84]. Most local institutional ethics committees lack the expertise or capacity to oversee complex clinical trials effectively[85].

India's NRA participates in several international regulatory organizations, such as the South East Asia Regulatory Network and Developing Country Vaccine Regulators' Network. India is a participant of ICMRA, an observer in the ICH, and a vice-chair of the WHO member state mechanism on substandard and falsified medical products. CDSCO has also undertaken several mutual agreements and memoranda of understanding with the NRAs of the United States, the United Kingdom, Japan, Russia, and Sweden. Assessment of the Indian vaccine regulatory system using the WHO global benchmarking tool found the system to be functional at maturity level 4, which indicates an advanced level of performance and continuous improvement [86].

Table 1. India's drug regulatory agencies

Entity	Role
Central Drugs Standard Control Organization (CDSCO)	• Apex national regulatory authority in India, led by Drugs Controller General of India (DCGI) • Establishes policies for the implementation of provisions under Drugs and Cosmetics Act (1940) and Drugs and Cosmetics rules (1945). • Collaborates with WHO, U.S. FDA, EMA, PMDA, European Directorate for the Quality of Medicines, South Asian Association for Regional Cooperation, and BRICS* nations • Regulates import of drugs, including quality control, registration, and licensing
Central Drugs Laboratory	• National statutory laboratory of Indian government for quality control of drugs and cosmetics • Appellate authority in drug quality-related disputes • Procurement, preservation, and distribution of international reference standard pharmaceutical substances • Prepares and maintains national reference standards

Table 1. India's drug regulatory agencies (contd.)

Entity	Role
Food and drug administrations at state level	• Responsible for licensing of manufacturing sites for drugs, including active pharmaceutical ingredients and active formulation • Responsible for licensing of establishments for sale or distribution of drugs
National Pharmaceutical Pricing Authority	• Responsible for setting and revising prices of controlled bulk drugs and formulations of National List of Essential Medicine • Responsible for regulating the prices and availability of medicines under Drugs (Prices Control) Order (1995)
Department of Pharmaceuticals	• Supports development of pharmaceutical industry and oversees industry policy • Promotes research in pharmaceutical sector, development of infrastructure, education and training for technical guidance, and private-public partnerships
Indian Council of Medical Research (ICMR)	• Apex regulatory body that formulates, coordinates, and promotes biomedical research
Department of Biotechnology	• Apex regulatory body that oversees developments in modern biology and biotechnology through several health care R&D projects in India
Drugs Consultative Committee and Drugs Technical Advisory Board	• Provides technical guidance to CDSCO

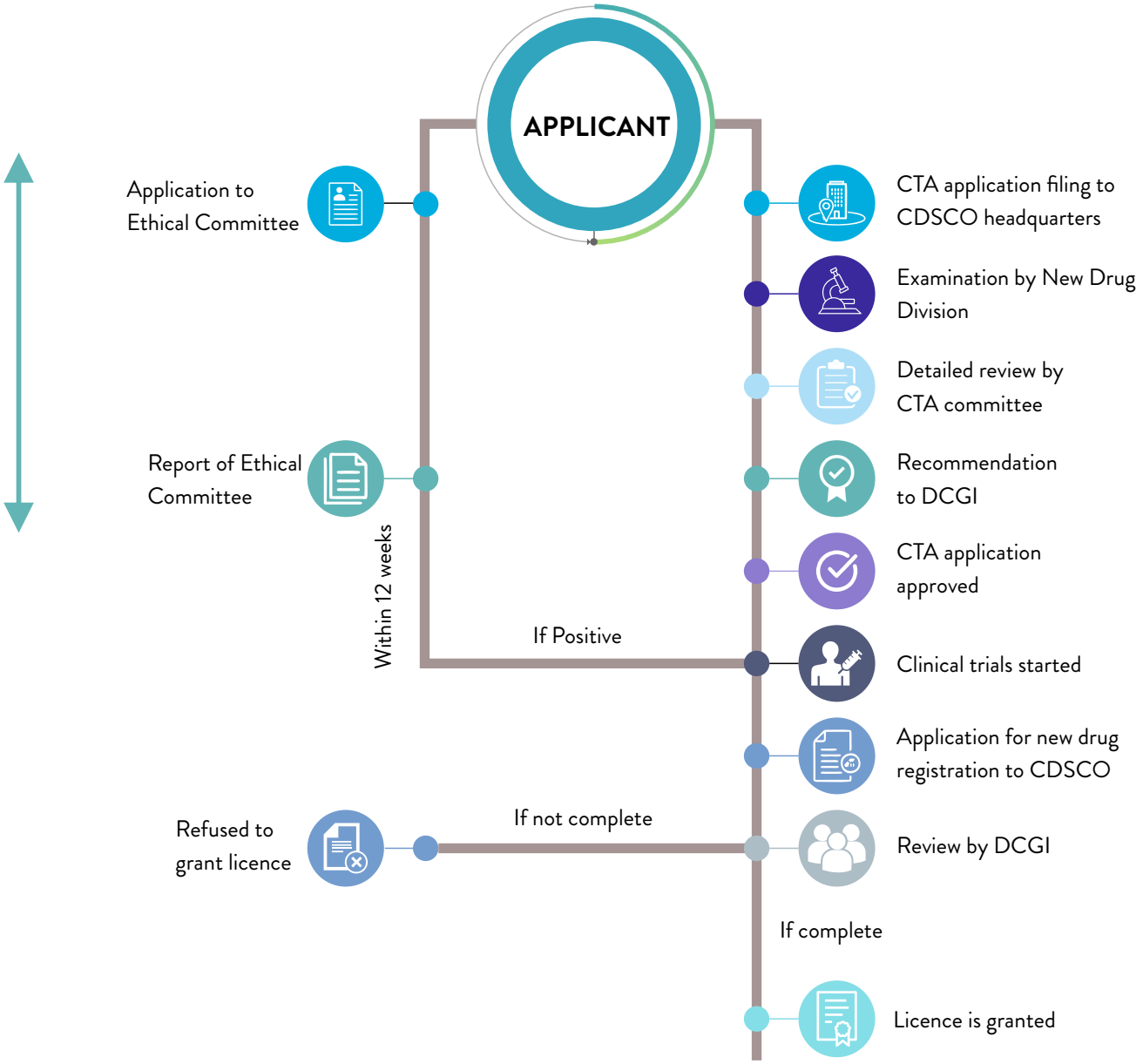
* BRICS: Brazil, Russia, India, China and South Africa.

Medicine registration

The Drugs and Cosmetics Act–1940 regulates India's import, manufacture, distribution, and sale of drugs. The Drugs and Cosmetics Act–1940 and the Drugs and Cosmetics Rules–1945 list provisions to prevent the manufacture of low-quality drugs, with definitions of adulterated and misbranded drugs to support any possible legal action. Over the years, various revisions and amendments have been implemented according to guidelines specified by international organizations such as WHO and ICH. The drug approval process in India starts when the manufacturer (applicant) submits a clinical trial application (CTA) at the CDSCO headquarters in New Delhi and applies to an independent ethics committee (Fig. 1). The clinical trial documents submitted to CDSCO are reviewed by the Independent Ethics Committee and the Institutional Review Board. Upon the DCGI approval, the clinical study needs to be registered online in the Clinical Trial Registry of India, a free online database for all ongoing clinical trials in India. The main objective of the registry is to improve transparency, internal validity and accountability, maintenance of ethical records, and results of the registered trials.

Figure 1: Drug Approval Process in India

Adapted from Anusha and Nagabhushanam, 2017[87]



For a clinical trial to commence, the applicant needs an approval letter from DCGI, trial registration in the Clinical Trial Registry of India, ethical approval, and insurance documents. Upon the trial's completion, a clinical study report with trial data is submitted to the DCGI. Clinical trial sponsors are also required to obtain a license for manufacturing and sale or importation and sale within the country.

Clinical trials for NCEs approved and marketed in the European Union, the United Kingdom, Australia, Canada, Japan, or the United States, as part of a global clinical trial (Phase III) or registration trial, need to be conducted locally to generate evidence of safety and efficacy in the Indian population. However, recent changes, introduced in the New Drugs and Clinical Trials Rules–2019 (2019-CTRules), provide flexibility that can expedite approvals for new drugs targeting diseases of particular relevance to India, unmet medical needs, and public health emergencies[88]. Under these provisions and subject to certain conditions, the requirement for Phase III clinical trials is waived for drugs approved in other countries; companies can be asked to conduct Phase IV trials to validate the anticipated safety and efficacy of the drug in the Indian population[88]. Additional flexibility and waiving of the requirement for a Phase IV trial may apply to orphan drugs, drugs available at a high cost, or those indicated for a life-threatening disease, extensively drug-resistant TB, hepatitis C, H1N1, dengue, and malaria; however, this exception is rarely used[89,90].

Lessons from the COVID-19 pandemic

During the COVID-19 pandemic, regulatory authorities in India responded swiftly by adopting new guidelines and making their regulatory framework more agile to support COVID-19 vaccine development and clinical trials[91]. Efforts to optimize regulatory processes and reduce approval timelines are now picking up pace. In October 2021, the Department of Pharmaceuticals and Ministry of Chemicals and Fertilizers developed a "Draft policy to catalyze research & development and innovation in the Pharma-Medtech sector in India"[92]. In a section on improving regulatory processes and frameworks for drug approvals, the draft policy outlines a procedure pathway with checklists, prescribed timelines, parallel processing, and data sharing across regulators; a digital portal to enable automated document management workflows to allow transparency and half regulatory approval time for innovative products; an increase in regulatory capacity; and review of legislation related to R&D of pharmaceuticals and medical devices to remove inconsistencies and redundancies[92].

Opportunities for antimicrobial innovation

Best practices

- Regulatory authorities in India have drafted a plan to strengthen regulatory capacity and reduce the time to drug approval by optimizing the process, adopting digital platforms, and updating current legislation.
- The 2019–CTRules include flexibilities in which Phase III and sometimes Phase IV clinical trial requirements can be waived for drug categories addressing public health needs, based on the approvals granted in other recognized NRAs.

Recommendations

- Create a category for antimicrobials targeting serious or life-threatening infections within the regulatory framework, formally making antibiotics eligible for the expedited processes allowed under the 2019-CTRules.
- Create a committee of regulatory experts focusing on AMR-related issues and improve coordination among regulatory entities.
- Create an antibiotic clinical trial network to promote collaboration with national and international stakeholders and support the conduct of complex clinical trials.

Conclusion

An analysis of the regulatory frameworks for drug approval in South Africa, Brazil, and India reveals a common theme: the need for regulatory system strengthening, which may be achieved by adopting technology-driven solutions, increasing human resource capacity, and creating opportunities for regulatory reliance in agency approvals. Barriers to the timely evaluation of applications include heavy dependence on external assessors, lack of internal coordination, and lack of early application support. Although national regulatory authorities in Brazil, South Africa, and India have adopted some risk-based approaches that can expedite the drug approval process, the inclusion of antimicrobials targeting serious or life-threatening infections in the regulatory framework for these pathways could further support the development and licensure of new antibiotics. Experts interviewed for this analysis observed that antimicrobial resistance had received political attention in recent years but that competing public health emergencies, including the COVID-19 pandemic, have prevented its translation into action. As mature regulatory organizations work toward harmonization and alignment, the inclusion of these three countries' regulatory authorities in bilateral and multilateral collaborations can provide valuable perspectives for regulatory innovations at the global level.

Lessons from the COVID-19 pandemic demonstrate what can be achieved through collaboration and harmonization when a country faces a public health emergency. At the start of the pandemic, members of the International Coalition of Medicines Regulatory Authorities pledged to strengthen global cooperation and prioritize COVID-19 clinical trials[93]. To deal with shortages in essential products, support vaccine development, and conduct clinical trials under pandemic conditions, regulatory agencies had to improve national and international collaborations and adopt fast-track pathways and digital technologies. The international community should leverage this momentum to address other global health threats. Global initiatives, such as the WHO's R&D Blueprint for Action to Prevent Epidemics and the Global Research Collaboration for Infectious Disease Preparedness, could serve as models for collectively addressing the threat of antimicrobial resistance.

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What We Do
We live in an interconnected world: the health and well-being of the environment, animals, and humans are intertwined in ways that are becoming increasingly apparent. Tackling today's greatest challenges—whether climate change, pandemics, or drug resistance—requires an approach that recognizes these relationships.

The One Health Trust (OHT) uses research and stakeholder engagement to improve the health and well-being of our planet and its inhabitants. OHT continues and builds on the work of the Center for Disease Dynamics, Economics & Policy (CDDEP), which for more than a decade has conducted vitally important research on major global health challenges, including Covid-19, antimicrobial resistance, hospital infections, tuberculosis, malaria, pandemic preparedness and response, vaccines, medical oxygen shortages, and noncommunicable diseases. OHT's work now expands to take on issues related to climate change, biodiversity protection, and the effect of changing human diets on the planet.

At OHT, we believe that answers to the world's most critical questions lie between disciplines. Accordingly, our researchers employ a range of expertise—from economics, epidemiology, disease modeling, and risk analysis to clinical and veterinary medicine, geographic information systems, and statistics—to conduct actionable, policy-oriented research.

OHT has offices in Washington, D.C., and Bangalore, India, with researchers based in North America, Africa, and Asia. Our projects lead to policy recommendations and scientific studies published in leading journals. We are experienced in addressing country-specific and regional issues as well as global challenges. Our research is renowned for innovative approaches to design and analysis, and we communicate our work to diverse stakeholders.