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# Assessment of Regulatory Requirements and Filling Procedure of Drug Master File for Brazil, Europe, and India, USA and Australia

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**A B S T R A C T**

For a new drug, the FDA commits to reviewing most NDAs/BLAs within a total of 12 months. Once a drug is initially approved to treat a specific population or indication, applicants may conduct additional clinical studies to support subsequent FDA approvals in other settings (e.g., in another line of therapy), in combination with other treatments, or in other diseases. For a subsequent marketing application for additional use of an approved drug, the appropriate nonclinical and CMC data may have already been reviewed by the Agency in the initial application; as a result, supplemental marketing applications typically contain less data. Accordingly, the FDA aims to review supplemental applications within a total of 10 months. The study aims to assess the regulatory requirements and filing procedure of drug master file for brazil, europe, India, USA and Australia. New drugs begin in the laboratory with scientists, including chemists and pharmacologists, who identify cellular and genetic factors that play a role in specific diseases. They search for chemical and biological substances that target these biological markers and are likely to have drug-like effects. The Drug approvals in the India, Europe & US are the most thought due in the world. The primary purpose of the rules governing medicinal products in India, Europe & US is to safeguard public health. It is the role of public regulatory authorities to ensure that pharmaceutical companies comply with regulations.

**Keywords:** FDA approvals, brazil, europe, India, USA and Australia, medicinal products, Public health.

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**C O N T E N T S**



## 1. Introduction

Once clinical trials have been initiated, generating the breadth and depth of data required to appropriately assess the benefit/risk of a new drug takes years of effort across multiple disciplines. In this tutorial, we discuss a range of programs implemented by global Health Authorities to expedite both drug development and Health Authority review of marketing applications. In the United States, the data package submitted to the US Food and Drug Administration (FDA) to support a marketing approval is called either a New Drug Application (NDA) for small-molecule drugs, or a Biologics License Application (BLA) for large-molecule drugs (biologics).1 In the European Union, the data package submitted to the European Medicines Agency (EMA) to support a marketing approval is called a Marketing Authorisation Application (MAA). Nonclinical data supporting the pharmacology and

toxicology of the drug, data on the drug's chemistry, manufacturing, and controls (CMC), and clinical safety and efficacy data from phase I through phase III programs are synthesized into one cohesive application describing the safety and efficacy profile of the drug in a given patient population. Once these data are generated, Health Authorities require time to evaluate whether the data provided support a marketing approval.

For a new drug, the FDA commits to reviewing most NDAs/BLAs within a total of 12 months. Once a drug is initially approved to treat a specific population or indication, applicants may conduct additional clinical studies to support subsequent FDA approvals in other settings (e.g., in another line of therapy), in combination with other treatments, or in other diseases1-4. For a subsequent marketing application for additional use of an approved drug, the appropriate nonclinical and CMC data may have already been reviewed by the Agency in the initial application; as a result, supplemental marketing applications typically contain less data. Accordingly, the FDA aims to review supplemental applications within a total of 10 months.

The data required to initiate first-in-human clinical trials. Once clinical trials have been initiated, generating the breadth and depth of data required to appropriately assess the benefit/risk of a new drug takes years of effort across multiple disciplines. In this tutorial, we discuss a range of programs implemented by global Health Authorities to expedite both drug development and Health Authority review of marketing applications.

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Under the centralized procedure, the EMA commits to reviewing both initial and subsequent applications for new indications, known as type II variations, within 210 days, which refers to the number of active review days at the EMA; this review clock stops while the applicant is generating responses to the EMA questions, so the actual review time may be much longer.

In the drug development world, for patients suffering from serious diseases and unmet medical needs waiting anxiously for new therapy options, the process of investigational therapy development and Health Authority application review time can feel exceptionally long. Global Health Authorities, including the FDA and EMA, have developed multiple mechanisms to expedite both the drug development process and marketing application review timelines for promising drugs intended to treat serious disease and unmet medical needs6-10.

US Food and Drug Administration (FDA) and European Medicines Agency (EMA) expedited programs. Note: Drugs may qualify for more than one expedited program. For US programs, drugs may be eligible for all of these programs, provided they meet the criteria. For EU programs, medicines may be eligible for most of these programs, if criteria are met.

**Decreasing drug development timelines**

Health authorities offer programs that enable more detailed feedback and closer collaboration with the agency, taking some of the guesswork out of submitting a marketing application. Fast Track Designation (United States), Breakthrough Therapy Designation (BTD; United States), and PRIority MEdicines (PRIME) Designation (European Union) are three such programs.

**Fast track (FDA)**

The FDA’s Fast Track program was initially introduced in 1997 as part of the Food and Drug Administration Modernization Act (FDAMA), and later amended in the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA). Fast Track is designed to facilitate and expedite the development of drugs to treat serious conditions and fill an unmet medical need.

Determining whether a condition is serious is a matter of judgment, but is generally based on whether the drug will have an impact on such factors as survival, day-to-day functioning, or the likelihood that the condition, if left untreated, will progress to a more serious one. AIDS, Alzheimer’s disease, heart failure, and cancer are obvious examples of serious conditions. Epilepsy, depression, and diabetes are also considered to be serious conditions11-15.

Filling an unmet medical need is defined as providing a therapy where none exists or providing a therapy that may

be potentially better than available therapy. Any drug being developed to treat or prevent a condition with no current therapy is clearly directed at an unmet need. However, in cases in which available therapies exist, a drug must demonstrate an advantage over existing therapies to be eligible for Fast Track designation, such as:

- Superior efficacy or effect/improved effect on serious outcomes.
- Superior safety or avoiding serious side effects of an existing therapy.
- Improved diagnosis of a serious condition, where early diagnosis may result in an improved outcome.
- Decreasing a clinically significant toxicity of an available therapy that is common and causes discontinuation of treatment.
- Ability to address emerging or anticipated public health need.
- Unlike BTD, Fast Track requests may use nonclinical data as evidence to demonstrate the above.
- A drug that receives Fast Track designation is eligible for some or all of the following:
- More frequent meetings with the FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval.

More frequent written communication from the FDA about issues such as the design of the proposed clinical trials and use of biomarkers. Rolling review, which means that a drug company can submit completed sections of its BLA/NDA for review by the FDA, rather than waiting until all sections are completed before the entire application can be reviewed. Fast Track designation requests are usually submitted to the Investigational New Drug (IND), and can be initiated at any time during the drug development process. The FDA will review the request and make a decision within 60 days of the request. All submissions to an IND remain confidential; the FDA does not disclose Fast Track submissions or decisions,5 unless the submission has been publicly disclosed or acknowledged by the applicant. Once a drug receives Fast Track designation, early and frequent communication between the FDA and applicant is encouraged throughout the entire drug development and review process.

**BTD (FDA)**

BTD, initially introduced in the FDASIA, is an expedited pathway to facilitate drug development in the United States. An investigational drug can qualify for BTD "…if the drug is intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant end points, such as substantial treatment effects observed early in clinical development."2 Unlike with Fast Track, investigational drugs will need preliminary clinical evidence to obtain BTD. To qualify for BTD, the drug should be intended to treat a serious condition and should demonstrate the potential for substantial improvement over existing therapies. It is important to note that the BTD designation is also available for new indications for already approved drugs16-20.

**The following are examples of clinical evidence that could support BTD:**

- Direct comparison of the investigational drug to available therapy demonstrates a substantial benefit on a clinical end point.
- If no existing therapy exists, comparison of the investigational drug to placebo/historical control shows in a substantial effect on a clinically meaningful end point.
- The investigational drug in combination with available therapy demonstrates a much greater clinical response than available therapy.
- The investigational drug has a substantial effect on the underlying cause of disease in instances where available therapy is perceived to be a symptomatic treatment.
- The investigational drug reverses or inhibits disease progression in instances where available therapy only provides symptomatic benefits.
- The investigational drug has a better safety profile than available therapy with a similar efficacy profile.

The FDA can rescind BTD later in development if the drug no longer meets the above criteria. For example, the FDA rescinded BTD for Tonix Pharmaceuticals' Tonmya (cyclobenzaprine HCl) and Trevana's oliceridine due to the lack of appropriate clinical or safety data needed to support continuation of the designation.

Benefits of obtaining a BTD include increased interaction and guidance from the FDA during drug development and review. Specifically, senior FDA managers are involved in discussions and reviews, along with an assigned cross-disciplinary project lead, to provide thorough guidance to ensure efficient drug development. In addition, the applicant can submit parts of the marketing application for a drug granted BTD on a rolling basis, potentially expediting time to approval.

The applicant can submit the request for BTD, which must include appropriate supportive preliminary clinical evidence, at the time of the IND submission or any time before marketing approval, ideally before the End-of-Phase 2 meeting; however, the FDA has made it clear since the initiation of the BTD program that it expects to see potentially "game changing" clinical data to support a BTD application. The FDA response is expected within 60 calendar days of receipt of the request. As with Fast Track designation, the FDA does not publicly disclose any information about BTD requests or status.

## 2. Methodology

New drugs begin in the laboratory with scientists, including chemists and pharmacologists, who identify cellular and genetic factors that play a role in specific diseases. They search for chemical and biological substances that target

these biological markers and are likely to have drug-like effects. Out of every 5,000 new compounds identified during the discovery process, approximately five are considered safe for testing in human volunteers after preclinical evaluations. After three to six years of further clinical testing in patients, only one of these compounds on average is ultimately approved as a marketed drug for treatment.

The drug approval process varies from one country to another. In some countries, only a single body regulates the drugs and responsible for all regulatory tasks such as approval of new drugs, providing license for manufacturing and inspection of manufacturing plants e.g. in USA, FDA performs all the functions. However in some counties all tasks are not performed by a single regulatory authority, such as in India, this responsibility is divided on Centralized and State authorities. Worldwide, federal, state, and local regulatory agencies work to assure licensing, registration, development, manufacturing, marketing and labeling of pharmaceutical products so that they are in compliance with all applicable rules.

## 3. Results and Discussion

### Brazil

Brazilian Health Surveillance is the regulatory authority responsible for the review and approval of clinical trial applications for registered and unregistered drugs. ANVISA is attached to the Ministry of Health (MOH), which grants it the authority to regulate food and drug laws in Brazil. A clinical trial application is referred to as the Drug Clinical Development Dossier or Dossier Desenvolvimento Clínico de Medicamento (DDCM) and ANVISA's approval of the DDCM is known as a Special Notice/Bulletin or a Comunicado Especial (CE). Brazil has a centralized registration process for the ethics committee (ECs) and has a national ethics committee (CONEP) and local ethics committees (CEP). The Institutional ethics committee (IEC) – known as a Comitê de Ética em Pesquisas (CEP) will review and approve all clinical trial applications prior to ANVISA initiating its review and approval process. The National Commission for Ethics in Research (CONEP) is the central statutory body responsible for the registration, audit, and accreditation of Institutional ethics committees (ECs), known as (Committees of Ethics in Research (Comitês de Ética em Pesquisas) (CEPs) and is the advisory body for the Ministry of Health (MOH). Applications with coordination or sponsorship originating outside of Brazil require an additional EC review by the National Commission for Ethics in Research (Comissão Nacional de Ética em Pesquisa) (CONEP).

### USA

The safety and efficacy standards for new drug product approval. To receive approval for marketing, a sponsor must show that a new drug is safe and effective.18 To establish effectiveness, the sponsor must present "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended. By its terms, § 505(d) of the FDCA permits FDA to find that data from one adequate and well-controlled clinical investigation and confirmatory evidence constitutes substantial evidence of effectiveness, but FDA has typically only applied this provision where the lone study was statistically significant at a very high level or for products addressing orphan diseases, where more than one trial is not logistically feasible. In determining whether an investigation is adequate and well-controlled, FDA considers specific characteristics, including whether the study design permits a valid comparison between the investigational drug and the control to permit quantitative assessment of the drug's effect and whether the recruitment, allocation to treatment arms, observation of patients, and method of analysis permit inference, by, for example, limiting bias and assuring comparability.

A sponsor must also establish safety "for use under conditions prescribed, recommended, or suggested in the proposed labeling."24 Neither the statutes nor regulations governing marketing approval define safety. To assess safety, FDA uses a risk-benefit framework.25 This analysis weighs the benefits against the risks of approving a new compound and considers all of the evidence submitted regarding safety and efficacy, the type and severity of the condition the new compound addresses, other available therapies for that condition, and risk management tools that potentially could ensure the benefits outweigh the risks.

### Clinical trials and phases of drug development C.

To develop the evidence necessary to satisfy the FDCA's safety and efficacy requirements, sponsors use a series of pre-clinical and three pre-marketing human clinical trial phases.27 Each phase builds on data from the prior phases and examines a different component of the drug's mechanisms, safety, and efficacy.28 While the three human clinical trial phases are theoretically distinct experiments, some modern investigations have blurred the lines between them or excluded components altogether.

The process begins with preclinical research through in vitro (test tube) tests, tissue cell cultures, computer driven data analysis, and/or live animal models to obtain basic information about the new drug's toxicity, pharmacodynamics, and pharmacokinetics.30 If these studies appear sufficiently promising, the manufacturer files an Investigational New Drug (IND) Application to obtain an exemption from the FDCA's prohibition against shipping experimental drugs without FDA approval in interstate commerce and to allow FDA to assess the safety of the study.

After the submission of an IND, the investigator introduces the investigational drug to humans for the first time in Phase 1. These trials are small, typically composed of about twenty to eighty healthy individuals, and are not controlled.33 The investigator seeks to assess the safety (including significant short-term side-effects), toxicity, dosage range, and the pharmacokinetics of the investigational drug.34 Some studies may have an

extension component, in which the optimal dose determined from a dose escalation series is tested without controls in a group of study participants.

For those investigational drugs that survive Phase 1, the investigator then generally conducts a randomized, controlled trial of 80 to 200 subjects who have the disease or condition the drug is intended to treat.35 Phase 2 trials provide more information on safety, and, by testing on patients with the disease or condition of interest, these trials present the first data on the efficacy of the investigational drug and any dose-response relationships.36 The success of Phase 2 relies on the adequacy of the design of Phase 1. For example, if Phase 1 provided inadequate information on dosage levels, Phase 2 may test the investigational drug "for activity at too low or [too] high a dose."

In the usual case, the safety and efficacy data from these two phases do not in themselves satisfy FDA's requirements of "adequate tests by all methods reasonably applicable to show whether or not such drug is safe" and of "substantial evidence" of efficacy, making Phase 3 trials necessary. Phase 3 clinical trials are expanded controlled and uncontrolled studies.39 Phase 3 trials involve significantly more patients (on the order of hundreds to thousands of patients) and apply stricter exclusionary criteria to the patients who may enroll than Phase 2 trials.40 These trials provide more extensive data on safety and efficacy, including any side effects associated with long-term use, to enable FDA "to evaluate the overall benefit-risk relationship of the drug.

One particularly important component of Phase 3 trials is the primary endpoint used to measure the benefit from a drug product.42 Under the regular approval mechanisms, FDA approves New Drug Applications (NDAs) based on either a direct clinical efficacy endpoint or a validated surrogate endpoint. A clinical endpoint "is a characteristic or variable that directly measures a therapeutic effect of a drug—an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives." A clinical benefit "is a positive therapeutic effect that is clinically meaningful in the context of a given disease. The clinical benefit must be weighed against a treatment's risks to determine whether there is an overall benefit for patients (i.e., positive benefit-risk profile). Quintessential primary clinical efficacy endpoints include improved overall survival and symptomatic improvement (such as time to progression of cancer symptoms).

An intermediate clinical endpoint is a measure of how a patient feels or functions, but is not the ideal endpoint that a drug product seeks to affect.47 A surrogate endpoint is an alternative endpoint that measures the effect of a drug product on a distant biological marker that is predicted to relate with some degree of certainty to a clinical efficacy endpoint.48 A validated surrogate endpoint "is known to predict clinical benefit" for a certain disease state and for a certain type of intervention.49 It has been suggested that to be a validated surrogate endpoint, the biological marker "must be correlated with the clinical endpoint" and "must fully capture the net effect of the intervention on the clinical-efficacy endpoint" for a specific disease setting and class of interventions.50 Blood pressure reduction, for example, is a validated surrogate for risk of stroke in patients with cardiovascular disease for well-studied classes of antihypertensive agents such as beta-blockers and low-dose diuretics with known favorable safety profiles.

Following Phase 3 trials, a sponsor may submit an NDA seeking approval to market the compound. A sponsor also may conduct Phase 4 studies after FDA approves an NDA and the new drug enters the market. Phase 4 studies seek "to gather information on the drug's effect in various populations and any side effects associated with long-term use."

At various points during this development process, FDA and the sponsor of a new drug product may meet to discuss questions and issues that arise. For any type of new drug product, a sponsor may request meetings at the end of Phase 2 (EOP2 meeting) to discuss the safety of proceeding to Phase 3, the Phase 3 plan and protocol, and any additional information needed to support a marketing application, among other topics; they may also seek to meet with FDA prior to the submission of a NDA (pre-NDA meeting) to discuss any major unresolved problems, statistical analysis methods, and the best approach to formatting and presenting the data in the NDA.

Pressures on drug development and innovation: time and cost of full marketing approval for a new drug product D. The length and cost of the traditional development and approval process varies between products, and comparisons of the length of the development process across time periods are complicated by different methods of analysis and different data. But, there is nonetheless evidence and an accepted belief that both have been increasing. According to some estimates, in the 1960s and 1970s, clinical development of a new compound through marketing approval took respectively 7.9 years and 8.2 years, on average.55 Although one study assessing data for the 1980s and 1990s estimated that it had decreased to approximately 7.5 years, much of this reduction may have been due to shorter FDA approval times in the 1990s following the passage of the Pharmaceutical Development User Fee Act of 1992 (PDUFA), which established time goals for regulatory approval.56 Indeed, the length of the period between the start of clinical testing and submission of an NDA or biological licensing application (BLA) with FDA was on average six years (72.1 months) in the 1980s and early 1990s, 3.5 months longer than the same period in the 1970s and early 1980s. Another analysis suggested that the average development time from patent filing through market launch in the U.S. and 15 European Union countries spanned 9.7 years for products launched in the 1990s and increased to 13.9 years for those which began marketing in 2000 or later.

In addition to an increase in the length of clinical trials, the cost of developing new compounds has risen dramatically. According to one study led by DiMasi, the average out-of-pocket cost to develop a new compound that receives marketing approval by FDA, taking into account the costs of other failed research over the same time period, was $403 million (in 2000 U.S. dollars), or $802 million capitalized, for drugs first tested in humans between 1983 and 1994 and receiving marketing approval on or about 1997.59 The estimated total capitated cost was more than twice as high as that calculated by the author in an earlier study for drugs first tested in humans a decade earlier (between 1970 and 1982) and receiving marketing approval on or around 1984, which itself was more than twice as high as figures calculated for new compounds generally approved in the 1970s.60 Notably, evidence suggests that costs associated with time accounted for half of these total costs.61 Moreover, evidence indicates that clinical testing expenses significantly drive the increased costs of developing a new compound to marketing approval.

**EUROPE**

In general, the approval of medicines is harmonized in the European Union (EU). Besides a few national specifics, the approval is based on the principles laid out in the Directives and Regulations of the European Parliament and Commission. It is possible to get national approval in one of the member states; however, as soon as a company seeks approval in two or more member states they must use the EU procedures. In principle, there are three procedures for submitting a Marketing Authorization Application (MAA) in the EU: (1) the mutual recognition procedure (MRP); (2) the decentralized (DCP) and (3) the centralized procedure (CP). The submission strategy for a given product will depend on the nature of the product, the target indication(s), the history of the product, and the marketing plan.

The centralized procedure leads to approval of the product in all 27 EU member states and in Norway, Iceland and Liechtenstein. Submission of one MAA thus leads to one assessment process and one authorization that allows access to the market of the entire EU. The process of the centralized procedure is triggered when the applicant sends the letter announcing the intent to submit a MAA (letter of intent), which is usually done at least seven months prior to the targeted submission date. Dedicated submission dates for each month of the year are provided by the European Medicines Agency (EMA) on its website. The letter of intent also initiates the assignment of the Rapporteur and Co-Rapporteur, who are the two appointed members of the Committee for Human Medicinal Products (CHMP) representing two EU member states. The Rapporteur and Co-Rapporteur will assess the MAA and provide the CHMP with the result of their analysis, which will be the basis of the conclusions of the CHMP, i.e., questions for the applicant or positive opinion with subsequent decision on final approval by the commission. When using the MRP or DCP, the applicant must select which and how many EU member states in which to seek approval. In the case of an MRP, the applicant must initially receive national approval in one EU member state. This will be the so-called reference member state (RMS) for the MRP. Then, the applicant seeks approval for the product in other EU member states, the so-called concerned member states (CMS) in a second step: the mutual recognition process.

For the DCP, the applicant will approach all chosen member states at the same time. To do so, the applicant will identify the RMS that will assess the submitted MAA and provide the other selected member states with the conclusions und results of the assessment. In principle, the applicant can choose any EU member state as RMS; however, in almost all member states the applicants need to send a request for a time slot when they will be allowed to submit the application. Depending on the agency selected as RMS, the interval between submission of the request to the actual submission date can be two years or longer. Therefore, planning for the DCP well in advance is highly recommended.

In practice, the applicants are not completely free to decide which procedure is the most relevant. There are certain products, indications and conditions for which the centralized procedure is mandatory and not all products are eligible for this procedure. The centralized procedure is mandatory for three types of products as laid down in the Regulation 726/2004: (1) Medicinal products developed by means of one of the following biotechnological processes (e.g., recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, hybridoma and monoclonal antibody methods); (2) New active substances for which the therapeutic indication is the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorder, diabetes, auto-immune diseases and other immune dysfunctions, viral diseases and (3) Medicinal products that are designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000. Products such as advanced therapy medicinal products (ATMPs) and biosimilars fall under the mandatory scope.

Besides the products falling under the mandatory scope, the centralized procedure is also open for other innovative products. Examples are new active substances or other medicinal products that constitute a significant therapeutic, scientific or technical innovation, or the granting of a Community authorization for the medicinal product is in the interest of patients at Community level. The decision as to whether the product is eligible or not is made by the EMA upon the submission of the corresponding request (letter of eligibility) by the applicant. Since the centralized procedure focuses on innovative products, generics were not initially submitted. However, now that data exclusivity has ended for more and more products initially approved under the centralized procedure, the proportion of generics approved has increased recently.

**Indian Regulatory Approval Process**

The Indian regulatory approval process for drugs and

medical devices is a multi-step process that is designed to ensure the safety, efficacy, and quality of these products before they can be marketed and sold in India. The steps in the Indian regulatory approval process include: Pre-Clinical Studies: The first step in the approval process is the conduct of pre-clinical studies, which are conducted to evaluate the safety and efficacy of a new drug or medical device.

Clinical Trials: After the successful completion of pre-clinical studies, the next step is the conduct of clinical trials. Clinical trials are conducted to further evaluate the safety and efficacy of the drug or medical device in human subjects. New Drug Application (NDA): After the successful completion of clinical trials, the manufacturer must submit a New Drug Application (NDA) to the Central Drugs Standard Control Organization (CDSCO) for review and approval. The NDA must include data from pre-clinical studies and clinical trials, as well as information on the manufacturing process and the quality control measures in place.

Review and Approval: Once the NDA is received, the CDSCO will review the data and determine whether the drug or medical device is safe, efficacious, and of high quality. If the CDSCO determines that the product meets these standards, it will grant approval for marketing and sale in India. Post-Market Monitoring: After a drug or medical device is approved for marketing and sale, the CDSCO will monitor the product through post-marketing surveillance to ensure that it continues to be safe and effective. In conclusion, the Indian regulatory approval process for drugs and medical devices is designed to ensure the safety, efficacy, and quality of these products before they can be marketed and sold in India. The process involves a series of steps, including pre-clinical studies, clinical trials, submission of a New Drug Application, review and approval by the CDSCO, and post-market monitoring.

Australia: What are the requirements for ANVISA approval?

**Clinical research protocol**

Proof of Deposit Health Surveillance Rate (TFVS) (tax payment imposed on individuals and companies engaged in clinical research)

**Drug development plan**

Certified copy of the clinical agreement (contract or statement) that has been written, dated, and signed by the sponsor or his/her CRO

Ethics in Research Committee (ERC) (also known as a CEP) opinion issued for the first clinical trial center

**Investigator's Brochure (IB)**

Summary of investigational product's (IP's) safety aspects based on previous research in humans

Information on any discontinued development or withdrawal of IP.

**IP dossier**

Specific dossier for each clinical trial to be conducted in Brazil. Proof of clinical trial registration with the World Health Organization's (WHO) International Clinical Trials21-22.

**How to get approval?**

The Clinical Trial Application and associated documents (including the protocol, investigator brochure, informed consent form, and sponsor and institutional declarations), as well as all documentation provided to the CONEP/CEP System, must be translated into Portuguese. The Principal Investigator (PI) is responsible for submitting an application via the online Plataforma Brasil to the respective Institutional EC (CEP), and, if applicable, to the National Commission for Ethics in Research (Comissão Nacional de Ética em Pesquisa) (CONEP). For the multicenter clinical trial, the principal investigator (PI) shall submit a list of the participating institutions and the associated protocols as part of the research protocol package sent to the CEP for review. The CEP will review the protocol documentation for completeness which should be accomplished within 10 days following submission and shall issue an initial report 30 days from the date the protocol documents are fully accepted for review. CONEP (for which sponsorship or coordination originate outside of Brazil) must also review applications and shall issue its initial report for this additional review within 60 days from the date the documentation was accepted. Clinical Research Coordination on Drugs and Biologicals (Coordenação de Pesquisa Clínica em Medicamentos e Produtos Biológicos (COPEC) at ANVISA's office is responsible for conducting the review of clinical trial applications. All communication between the research center, the principal investigator, and the ethical committee system should be done through the online platform. Once approved by the Ethics committee application can be forwarded to ANVISA. ANVISA's approval of a clinical trial application is dependent upon obtaining proof of the EC's (CEP's) approval.

## 4. Conclusion

The Drug approvals in the India, Europe & US are the most thought due in the world. The primary purpose of the rules governing medicinal products in India, Europe & US is to safeguard public health. It is the role of public regulatory authorities to ensure that pharmaceutical companies comply with regulations. There are legislations that require drugs to be developed, tested, trailed, and manufactured in accordance to the guidelines so that they are safe and patient's well-being is protected23-25. Over the past years, a tendency has been seen for ICH members and beyond to modernize their regulatory systems to implement different expedited regulatory tools to ensure faster development and approval of innovative drugs in areas of unmet medical need. This has already resulted in new regulatory paradigms in major markets like China (providing BTD, priority review and conditional approval) and Brazil (now accepting less than comprehensive dossiers for rare diseases or diseases with unmet medical needs). MHRA by participating in the Project Orbis and Access Consortium as well as by establishing other innovative regulatory tools is able to approve certain medicines ahead of the European Union.

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