

## REVIEW ARTICLE

## PROCEDURE FOR DRUG APPROVAL IN DIFFERENT COUNTRIES: A REVIEW

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## ABSTRACT

Developing a new drug requires great amount of research work in chemistry, manufacturing, controls, preclinical science and clinical trials. Drug reviewers in regulatory agencies around the world bear the responsibility of evaluating whether the research data support the safety, effectiveness and quality control of a new drug product to serve the public health. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. This article focuses on history, regulatory policy and administration, and related issues with respect to different countries like U.S.A. , Europe ,China, Australia and India

**Keywords:** USFDA, EMA, TGA, Clinical trials, Approval stages

## INTRODUCTION

Currently different countries have to follow different regulatory requirements for approval of new drug. For marketing authorization application (MAA) a single regulatory approach is applicable to various countries is almost a difficult task. Therefore it is necessary to have knowledge about regulatory requirement for MAA of each country.

The new drug approval process consists of two stages (phases)- the first phase is for clinical trials and second phase is for marketing authorization of drug. Firstly, non-clinical studies of drug are completed to ensure safety and efficacy. The next step is the submission of application for conduction of clinical trials to competent authority of

respected country. In next step, clinical trials are carried out in four phases i.e. phase 1 – phase 4 study. These studies are carried out for the assurance of safety, efficacy and for optimization of dose of drug in human being. Then application for marketing of drug is carried out by competent authorities. The competent authority review the application and approve the drug for marketing purpose, only if that drug found to be safe and effective with desired effect as compare to adverse effect.

The following table indicates about the group of agencies working for drug approval procedure in their respected countries.

NAME OF COUNTRY	AGENCIES FOR DRUG REGULATION
USA	Centers for Disease Control and Prevention Department of Health and Human Services (DHHS) Fed World - US Government Information The Food and Drug Administration (FDA) National Center for Complementary and Alternative Medicine (NCCAM) National Institutes of Health (NIH) National Library of Medicine National Science Foundation Office of Disease Prevention
EUROPE	EU Legislation - Eudrax European Directorate for the Quality of Medicines and Healthcare (EDQM) European Medicines Agency (EMA) Heads of Medicines Agencies (HMA)
INDIA	Central Drug Standard Control Organization (CDSCO) Government of India Directory of Health and Family Welfare Indian Council of Medical Research (ICMR) Ministry of Health and Family Welfare
CHINA	State Food and Drug Administration (SFDA)
AUSTRALIA	Australia's Department of Health and Aged Care Therapeutic Goods Administration (TGA)

**USA:**

U.S. Pharmacopoeia was established in 1820 and Congress passed the original Food and drugs act, and signed by President Theodore Roosevelt. The Food and Drugs Act prohibits interstate

Commerce in misbranded and adulterated foods, drinks, and drugs. But in 1937, sulfanilamide tragedy occurred and due to which Federal Food, Drug and Cosmetic act was introduced and added new provisions including compulsion of showing safety of drug before its marketing. In 1962, The Kefauver- Harris Amendment Act was passed which require that manufacturers must prove that drug is safe and effective. Separate centers within the FDA regulate drugs, biologics, devices, and food.

An investigational new drug application (IND) outlines what the sponsor of a new drug proposes for human testing in clinical trials Phase 1 studies (typically involve 20-80 people) Phase 2 studies (typically involve a few dozen to about 300 people) . Phase 3 studies (typically involve several hundred to about 3,000 people) . The pre-NDA period, just before a new

drug application (NDA) is submitted, is a common time for the FDA and drug sponsors to meet Submission of an NDA is the formal step the FDA takes to consider a drug for marketing approval 8. After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed 9. If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness. The FDA reviews information that

goes on a drug's professional labeling (information on how to use the drug) 11. The FDA inspects the facilities where the drug will be manufactured as part of the approval process . FDA reviewers will approve the application or find it either "approvable" or "not approvable"

**Preclinical -**

Computer simulations, experimental animal studies, or *in vitro* studies are performed to

- identify a promising drug
- test for promising biologic effects
- test for adverse effects

A drug company may test many related compounds to identify 1 or 2 to take further in development. The FDA is not involved in this aspect of drug development but will review the study results for any compounds that are planned for clinical (human) testing.

**New Drug Application (IND)**

The IND – is the formal process by which a sponsor requests approval for testing of a drug in humans– includes information developed during preclinical testing regarding safety and effectiveness • Includes an "investigator brochure" that ensures that clinicians conducting the trial and their institutional review boards (IRBs) are adequately informed about possible effects of the drug.

There are 3 phases in clinical testing of a new drug

**Phase 1**

Phase 1 studies are usually conducted in healthy volunteers. The emphasis in Phase 1 is on safety. The goal is– to determine what the drug's most frequent side effects are often, to determine how the drug is absorbed, distributed, and excreted. The number of subjects typically ranges from 20 to 80.

**Phase 2**

The emphasis in Phase 2 is on effectiveness.

The goal of a Phase 2 study is to obtain preliminary data on whether the drug works in people who have a specific disease or condition• For controlled trials, patients receiving the drug are compared with similar patients receiving a placebo or a different drug • Safety continues to be evaluated and short-term side effects are studied. Typically, the number of subjects in Phase 2 studies ranges from a few dozen to about 300 after Phase 2.

At the end of Phase 2, the FDA and sponsors negotiate about how the large-scale studies in Phase3 should be done . The FDA usually meets with a sponsor several times, including prior to Phase 3 studies, and pre-NDA right before a new drug application is submitted.

**Phase 3**

Phase 3 studies begin if evidence of effectiveness is shown in Phase 2. Phase 3 studies are usually placebo-controlled – gather more information about safety and effectiveness – may test different dosages – may test the drug in different populations – usually include several hundred to about 3000 subjects – are often multi-center trials

**Clinical trials**

Clinical trials compare the new drug to a placebo or to an existing therapy• The standard for effectiveness may be statistical superiority to placebo or non-inferiority to an existing therapy• Adverse events are recorded, because trial populations are relatively small, only the most common adverse events may be discovered – also, clinical trial populations are healthier than real-world populations-- for example, a trial of an anti-depressant may exclude subjects with substance use disorder

**The New Drug**

The NDA – is the formal request by a sponsor to market a drug in the U.S. – includes the results of preclinical and clinical studies, manufacturing information, and labeling – can be hundreds of thousands of pages. The FDA has 60 days to decide whether to review the NDA

After deciding that it will review an NDA, the FDA has 10 months to make a determination (6 months for priority drugs) Application (NDA).

**NDA Decisions****Post marketing (Phase IV) Studies**

As part of the approval process, the FDA may obtain commitments from the sponsor to do

additional Phase 4 studies after the product is marketed. However, the FDA cannot enforce compliance. The FDA

also monitors adverse events through an adverse event surveillance program.

### Europe -

A sponsor has several options when seeking approval to market a new drug in Europe: a national authorization procedure, a decentralized procedure, a mutual recognition procedure, or a centralized procedure. Products that must use the centralized procedure include the following:

- ✓ all biologic agents or other products made using high-technology procedures
- ✓ products for HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions and viral diseases
- ✓ products for orphan conditions

### National authorization procedure

Each country within the EU has its own procedures for authorizing a marketing application for a new drug. A sponsor can consult the website of the regulatory agency in each country in which it is interested in obtaining marketing approval to obtain details of the approval process. A sponsor can also seek approval of several EU countries simultaneously using the decentralized or mutual recognition procedure.

### Decentralized procedure

For products that fall outside the scope of the European Medicines Agency (EMA) with regard to centralized procedures, a sponsor can submit under the decentralized procedure. Using this process, a sponsor can apply for simultaneous authorization in more than one EU country for products that have not yet been authorized in any EU country.

Mutual recognition procedure. With the mutual recognition procedure, a product is first authorized by one country in the EU in accordance with the national procedures of that country. Later, further marketing authorizations can be sought from other EU countries, who, rather than conducting their own review, agree to recognize the decision of the first country.

### Centralized procedure

European drug approvals are overseen by the European Medicines Agency. The EMA is a decentralized body of the EU, with headquarters in London, England. It is responsible for the scientific evaluation of applications for authorization to market medicinal products in Europe (via the centralized procedure). Marketing applications for drugs for use in humans are evaluated by the Committee for Medicinal Products for Human Use (CHMP).

Products that are eligible for review under the centralized procedure must meet the following criteria:

- ✓ biologic drugs developed by recombinant technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, and hybridoma and monoclonal antibody methods
- ✓ medicinal products containing new active substances for the following indications: AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune

diseases and other immune dysfunctions, and viral diseases

- ✓ orphan medicinal products

Other new active substances may, at the request of the applicant, be accepted for consideration under the centralized procedure when it can be shown that the product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a Community authorization is in the best interests of patients at the Community level.

### Pre-submission process

At least seven months prior to submitting a marketing authorization application (MAA), a sponsor must notify the EMA of their intention to submit and the month of submission. This pre-submission involves a variety of information including a document outlining the reasons the sponsor believes the application should fall under the centralized procedure. The EMA will consider the pre-submission and notify the sponsor of its decision regarding acceptance of the MAA.

### Selection of rapporteur/co-rapporteur -

The rapporteur is a country-specific regulatory authority within the EU. The rapporteur (reviewer) and co-rapporteur (if needed) are identified from the CHMP members. The selection of the rapporteur is based on objective criteria, to ensure objective scientific opinion and the best use of available expertise at the EMA. The role of the rapporteur is to perform the scientific evaluation and prepare an assessment report to the CHMP. If a co-rapporteur is involved, the co-rapporteur will prepare an independent assessment report, or provide a critique of the rapporteur's report, at the discretion of the CHMP. The process for assigning the rapporteur/co-rapporteur is usually initiated at the CHMP meeting following the receipt of a letter of an intention to submit. The sponsor is notified of the rapporteur/co-rapporteur once the EMA has deemed a submission admissible.

### Product naming

A sponsor's name for the drug product should be the same in all countries within the EU, except where it violates trademark rules. The sponsor should submit the proposed name in advance (usually four to six months, and not more than 12 months) of the marketing authorization application.

### China-

Economic reformation in China has been ongoing for almost three decades, creating opportunities for rapid growth in many areas including pharmaceutical industry. Drug research and development in China went through a revolutionary change during this period as indicated by the large number of scientific institutes for drug research, the impressive depth of drug research in many therapeutic areas and the rapidly increasing number of new drugs. A new era of drug research and development is on the horizon with the introduction of new scientific breakthroughs, such as biomarkers and pharmacogenomics. A unique drug evaluation system is needed in China not only to keep up with the scientific

development in drug research and development but also fit into the current overall economic environment in China.

#### Standard Procedure -

Currently, there are five types of drug registration application in China: New drug application, generic drug application, imported drug application, supplemental application and renewal application. For the first three types of application, there are two major stages that are under regulation in China: application to initiate clinical trials (including bioequivalent trials) and application to market or import a drug. According to the Drug Administration Law, approval by SFDA is required before clinical trials can be conducted in China or new drugs can be marketed in or imported into China. The detailed application procedure and review process for these two stages are outlined in the 2007 version of Drug Registration Regulations. For supplemental application, the review process will depend on the magnitude of change in the product and the specific application documents. Clinical trials are required if necessary. For renewal application, each approved drug should be re-evaluated after 5 years and the renewal approval will depend on whether the post-marketing data suggest serious drug safety issues or not during the last 5 years. Overall, the review processes for these applications in CDE are similar to those implemented by US FDA. There are review teams that are made of reviewers with expertise in different disciplines. The review team is responsible for evaluating whether the submitted data and documents support the safety and efficacy of the new drug as indicated. During the review process, reviewers may interact with external experts and the drug developers to reduce the uncertainty about the drug's safety and effectiveness based on the submitted information. The final decision for approval will be based on the risk/benefit balance for a specific indication after all the submitted information for the new drug is integrated during the drug evaluation process. For new molecular entities that are developed for serious or life-threatening diseases or diseases for which there is no available treatment, there exists fast track evaluation to accelerate the evaluation process (Yin, 2006). But based on the short history of twenty-five years (from 1984 to 2009) and the large number of applications the drug evaluation system in China is different from any other countries'. It has its own characteristics with the quality control of the review, open-minded review, promoting research within CDE and integrating the post-marketing review.

#### India

The Drug and Cosmetic Act 1940 and Rules 1945 were passed by the India's parliament to regulate the import, manufacture, distribution and sale of drugs and cosmetics. The Central Drugs Standard Control Organization

(CDSCO), and the office of its leader, the Drugs Controller General (India) [DCGI] was established. In 1988, the Indian government added Schedule Y to the Drug and Cosmetics Rules 1945. Schedule Y provides the guidelines and requirements for clinical trials, which was further revised in 2005 to bring it at par with internationally accepted procedure. The changes includes, establishing definitions for Phase I-IV trials and clear responsibilities for investigators and sponsors. The clinical trials were further divided into two categories in 2006. In one category (category A) clinical trials can be conducted in other markets with competent and mature regulatory systems whereas the remaining ones fall in to another category (category B) Other than A. Clinical trials of category A (approved in the U.S., Britain, Switzerland, Australia, Canada, Germany, South Africa, Japan and European Union) are eligible for fast tracking in India, and are likely to be approved within eight weeks. The clinical trials of category B are under more scrutiny, and approve within 16 to 18 weeks.

An application to conduct clinical trials in India should be submitted along with the data of chemistry, manufacturing, control and animal studies to DCGI. The data regarding the trial protocol, investigator's brochures, and informed consent documents should also be attached.

A copy of the application must be submitted to the ethical committee and the clinical trials are conducted only after approval of DCGI and ethical committee. To determine the maximum tolerated dose in humans, adverse reactions, etc. on healthy human volunteers, Phase I clinical trials are conducted. The therapeutic uses and effective dose ranges are determined in Phase II trials in 10-12 patients at each dose level. The confirmatory trials (Phase III) are conducted to generate data regarding the efficacy and safety of the drug in ~ 100 patients (in 3-4 centers) to confirm efficacy and safety claims. Phase III trials should be conducted on a minimum of 500 patients spread across 10-15 centers, If the new drug substance is not marketed in any other country. The new drug registration (using form # 44 along with full pre-clinical and clinical testing information) is applied after the completion of clinical trials. The comprehensive information on the marketing status of the drug in other countries is also required other than the information on safety and efficacy. The information regarding the prescription, samples and testing protocols, product monograph, labels, and cartons must also be submitted. The application can be reviewed in a range of about 12-18 months. Figure represents the new drug approval process of India. After the NDA approval, when a company is allowed to distribute and market the product, it is considered to be in Phase IV trials, in which new uses or new populations, long-term effects, etc. are explored.

Table 1: Drug Approval Stages in India

	Clinical Trials								
	Preclinical testing		Phase I	Phase II	Phase III		FDA		Phase IV
Years	3.5		1	2	3		2.5	12 total	Additional Post marketing testing required by FDA
Test Population	Laboratory and animal studies	File IND at FDA	20- 80 Healthy volunteer	100-300 patient volunteers	1000-3000 patient volunteers	File NDA at FDA	Review process / Approval		
Purpose	Assess safety and biological activity		determine safety and dosage						
Success Rate	5,000 compounds evaluated		5 enter trials					1 approved	

**Australia-**

The Therapeutic Goods Administration is a Commonwealth Government agency that regulates medical devices and drugs. Prescription medicines and over-the-counter medicines which meet Australian standards of quality, safety and efficacy are included on the Australian Register of Therapeutic Goods. Medicines may be registered or listed. Registered products are thoroughly evaluated and are labelled with an AUST R number.

The TGA administers the Therapeutic Goods Act 1989, the objects of which include 'a national system of controls relating to the quality, safety, efficacy and timely availability of therapeutic goods that are used in Australia, whether produced in Australia or elsewhere, or exported from Australia'. These activities are fully funded by fees charged for assessments, annual registrations and inspections.

**AUST R products**

Medicines that are registered include:

- ✓ Almost all prescription medicines
- ✓ A number of products, such as vaccines, which although not classified in law as needing a prescription warrant detailed evaluation
- ✓ Almost all conventional over-the-counter medicines
- ✓ A very small number of complementary medicines where the TGA has been satisfied that specific claims of efficacy in treatment or prevention of a disease are supported by adequate evidence.

**Prescription medicines**

The Australian system for the pre-registration evaluation of new active substances, as well as such things as new routes of administration and the extensions of approved uses ('indications') of already marketed products, has evolved since it was established in 1963. Most prescription medicines in use currently have been evaluated through this system. Nowadays an application for registration of a new active substance must be supported by extensive information about the synthesis of the substance, the

method of manufacture of the dose forms, studies of its pharmacology and toxicology in animals and clinical trials in humans demonstrating the efficacy and safety of the product in its proposed use. In addition, certification that manufacture has complied with Good Manufacturing Practice is obligatory. Registration in Australia does not expire. A product remains registered unless there are grounds for cancellation or the sponsor ceases marketing. A small number of active substances, such as aspirin, were supplied in Australia long before any evaluation process was in place. Their registration is not reviewed unless a safety issue arises or a change in use is proposed.

Many of the prescription medicines used in Australia are versions of the innovator product, usually produced by other manufacturers. These generic products are subject to the same regulation of manufacture and quality standards. However, only evidence that the formulation is bioequivalent to the innovator product is required, rather than a full demonstration of efficacy and safety. Bioequivalence studies usually involve a comparative study of the product in human volunteers, but benchtop testing of dissolution may suffice for some products. Similar testing in human volunteers is required to support the claims of modified-release formulations.

**Over-the-counter medicines**

Nowadays, almost all active substances in non-prescription medicines first enter the market as ingredients of prescription medicines. To assess whether or not an active substance is suitable for use in a non-prescription medicine usually requires the substance to have been used for at least two years as a prescription medicine. Not all active substances make the transition from prescription to over-the-counter use. The volume of new information to support efficacy and safety is usually less, because the registration of the over-the-counter product can draw on the accumulated experience as a prescription product. New over-the-counter products are assessed by the TGA for quality, efficacy and safety. The standards for such things as quality and circumstances of manufacture are essentially the same as those of prescription medicines.

**AUST L products**

The group of medicines that are listed consists almost entirely of complementary medicines. These include herbal medicines, most vitamin and mineral supplements, other nutritional supplements, traditional medicines such as Ayurvedic medicines and traditional Chinese medicines, and aromatherapy oils. This category of listed products came into effect in 1991 as a means of regulating products that seemed by their nature to have a low risk of causing adverse effects. Similar requirements for manufacture, including certification of Good Manufacturing Practice, apply as to AUST R products, but they are not evaluated before inclusion in the ARTG. The principal mechanism for ensuring that these products are safe is through the requirements of the Therapeutic Goods Regulations 1990. AUST L medicines must:

- not contain substances that are prohibited imports, come from endangered species or be covered by the national regulations which control access to many substances (Standard for the Uniform Scheduling of Drugs and Poisons)
- Conform to lists of permitted ingredients (minerals, vitamins, declared listable substances).
- In some instances, there are additional requirements such as dose limits, specified label warnings and limits on plant parts or methods of preparation. Certain herbs are not permitted.
- The initial approach to regulation of AUST L products did not require evidence to support manufacturers' claims, provided the products were not for the treatment of serious illnesses.

A concern that multiple and at times improbable claims were being made about products led to the introduction in April 1999 of a requirement that sponsors of AUST L products must hold evidence to substantiate their claims. This evidence may be called for and evaluated by the

TGA, should a concern or complaint arise at any time during the life of a product. If the evidence is inadequate, the TGA may cancel the listing for the product. A random sample of approximately 20% of new listings is assessed in detail for compliance with the listing requirements.

In 2003 an expert committee recommended that sponsors of AUST L medicines should submit summaries of the evidence they hold to support the efficacy of their products, and that the TGA should randomly audit this information.<sup>3</sup> Where there is evidence to support the efficacy of an AUST L medicine in a serious illness, registration (AUST R status) can be sought.

**Exemptions**

Medicines (except for gene therapy) that are dispensed or extemporaneously compounded for a particular person are currently exempt from TGA regulation. Some clinics and pharmacists are using this exemption as a means for supplying very large numbers of patients with medicines made in those pharmacies. On occasions, claims about special characteristics such as 'slow release product' are made. Such products are not assessed or regulated by the TGA. Similar exemptions apply to medicines individually dispensed by traditional Chinese medicine and homeopathic practitioners. Some other medicines are also exempt from the requirement for inclusion in the ARTG. Perhaps the most important are homeopathic medicines. This exemption from TGA regulation has seen the marketing of such purported homeopathic products as homeopathic somatropin and homeopathic melatonin. Increased TGA regulation of homeopathic products has therefore been recommended.<sup>3</sup> This might be expected to focus on ensuring that such products are formulated with regard to homeopathic principles and practices and are made in compliance with the same manufacturing requirements as conventional medicines.

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