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New Drug Approval Procedure in Different Countries: A Review

Preeti Maan Singh*, Shilpa Pahwa, Sheetl Chaudhary & Vandana Arora Sethi

School of Pharmacy, Lloyd Institute of Management & Technology Greater Noida, Uttar Pradesh, India

Abstract : Today, the regulatory requirements for approval of a new drug in the various countries of the world are quite different. To develop one single regulatory approach for marketing authorization application (MAA) of a new drug product for various countries is utmost difficult task- especially for companies with global activities.
Therefore, it is very important to know in detail the regulatory requirements in each country where an MAA should be submitted to establish a suitable regulatory strategy before the submission in order to avoid any major difficulties. The new drug approval is of two phase process, clinical trials phase & Marketing authorization of drug. The review article is based on the procedures for drug approval in different countries like India, USA, Australia, China, Turkey, Canada and European countries.
Keywords : New drug approval, Drug Approval procedure, Approval stages, USFDA.

Introduction

The drug approval process in India has faced challenges in recent years, some around compulsory licensing of patents, Govt. price control and narrow standards for patentability.[1]

The high cost of drugs limits access to health care around the world regulatory agencies play a crucial role in providing access to and monitoring the cost of drugs. Each government has its own regulatory process with the goal of providing high quality, affordable care to its citizens. In India the central regulatory agency is the drug controller general of India (DCGI), which works under the central drugs standard control organization (CDSCO).[2]

CDSCO & DCGI: the CDSCO is the central authority that oversees monitoring of drugs as per the Drugs and Cosmetics Act. The major functions of CDSCO are controlling drug imports, approving drug development and clinical trials, and monitors Drug Consultative committee and Drugs Technical Advisory Board meetings. DCGI is the main licensing authority, which directly issues permissions for new drug and devices as well as it oversees clinical trials as well. There is one special genetic engineering Approval Committee as well that approves r-DNA pharmaceutical products.[3]

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.

The review article is based on the procedures for drug approval in different countries like India, USA, Australia, China, Turkey, Canada and European countries.

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 date regarding the trial protocol, investigator's brochures, and informed consent documents should also be attached.

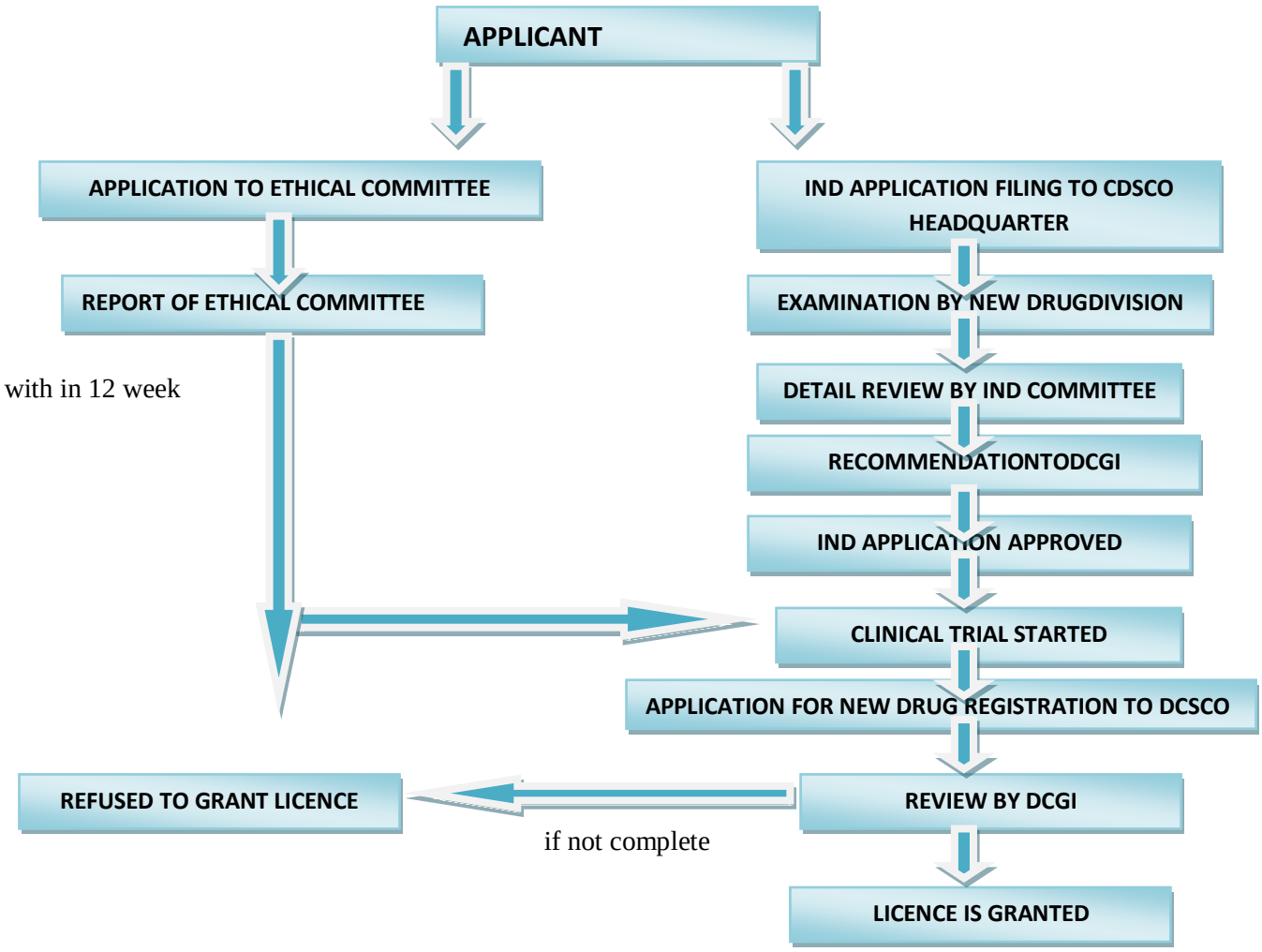


Figure 1: Flow chart for drug approval process in India [5]

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.[4]In view of the above procedural details, the regulatory approval procedure in India is outlined in Figure. 1

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 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.

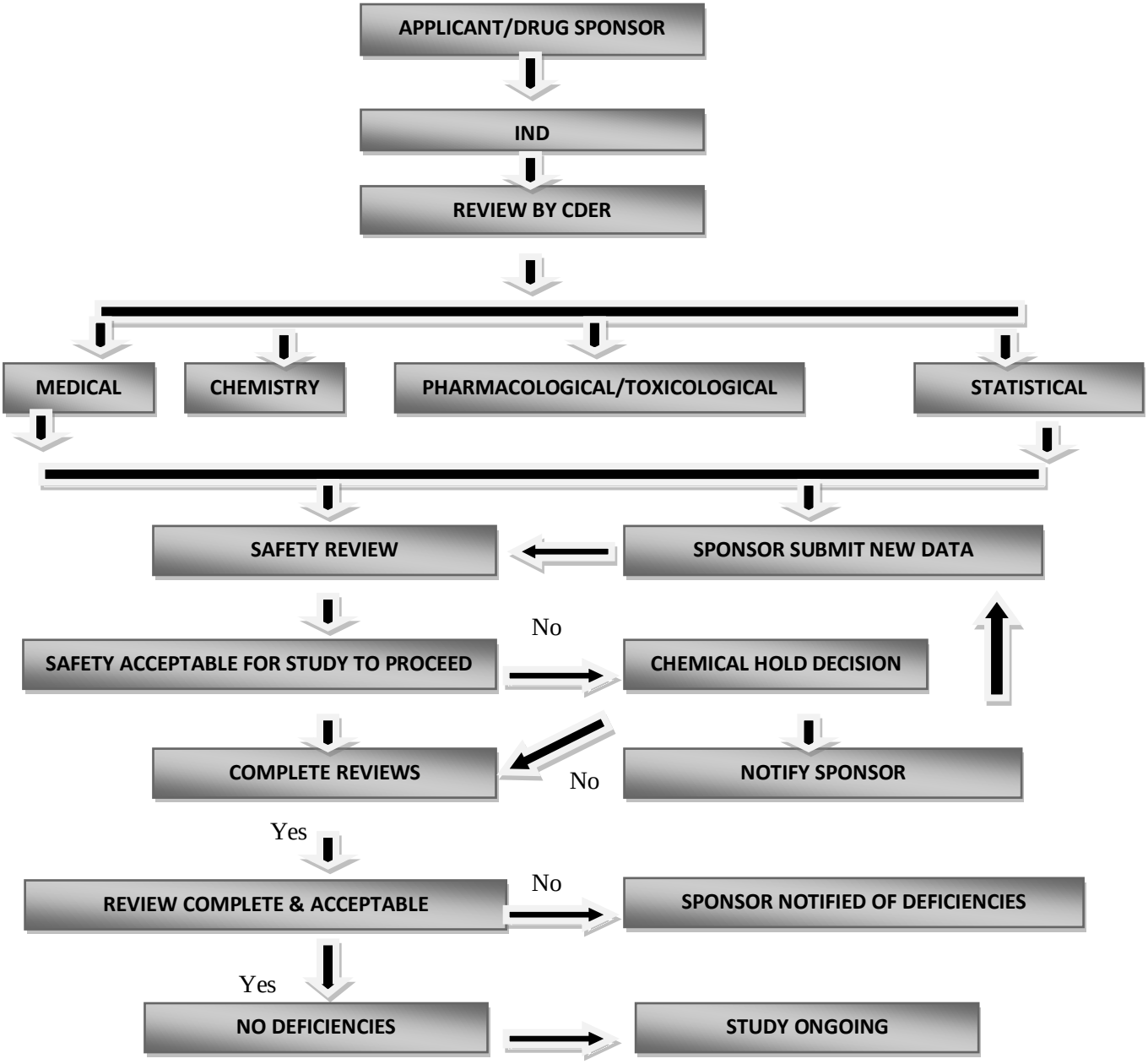


Figure 2: Investigational New Drug Application (IND)[6]

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.

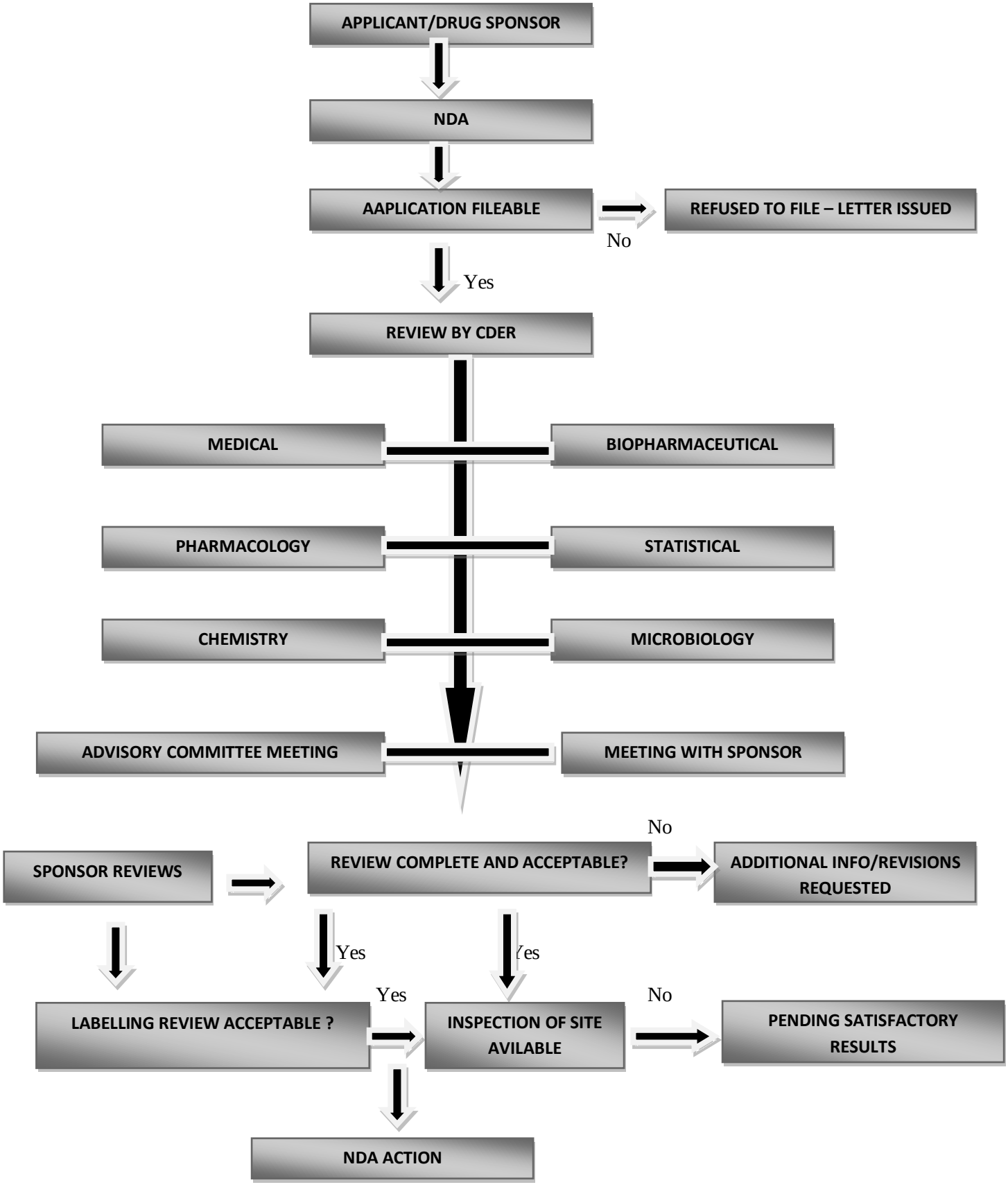


Figure 3:New drug Application NDA[6]

However, the FDA cannot enforce compliance. The FDA also monitors adverse events through an adverse event surveillance program.[4]In view of the above procedural details; the regulatory approval procedure in USA is outlined in Figures 2, 3 & 4.

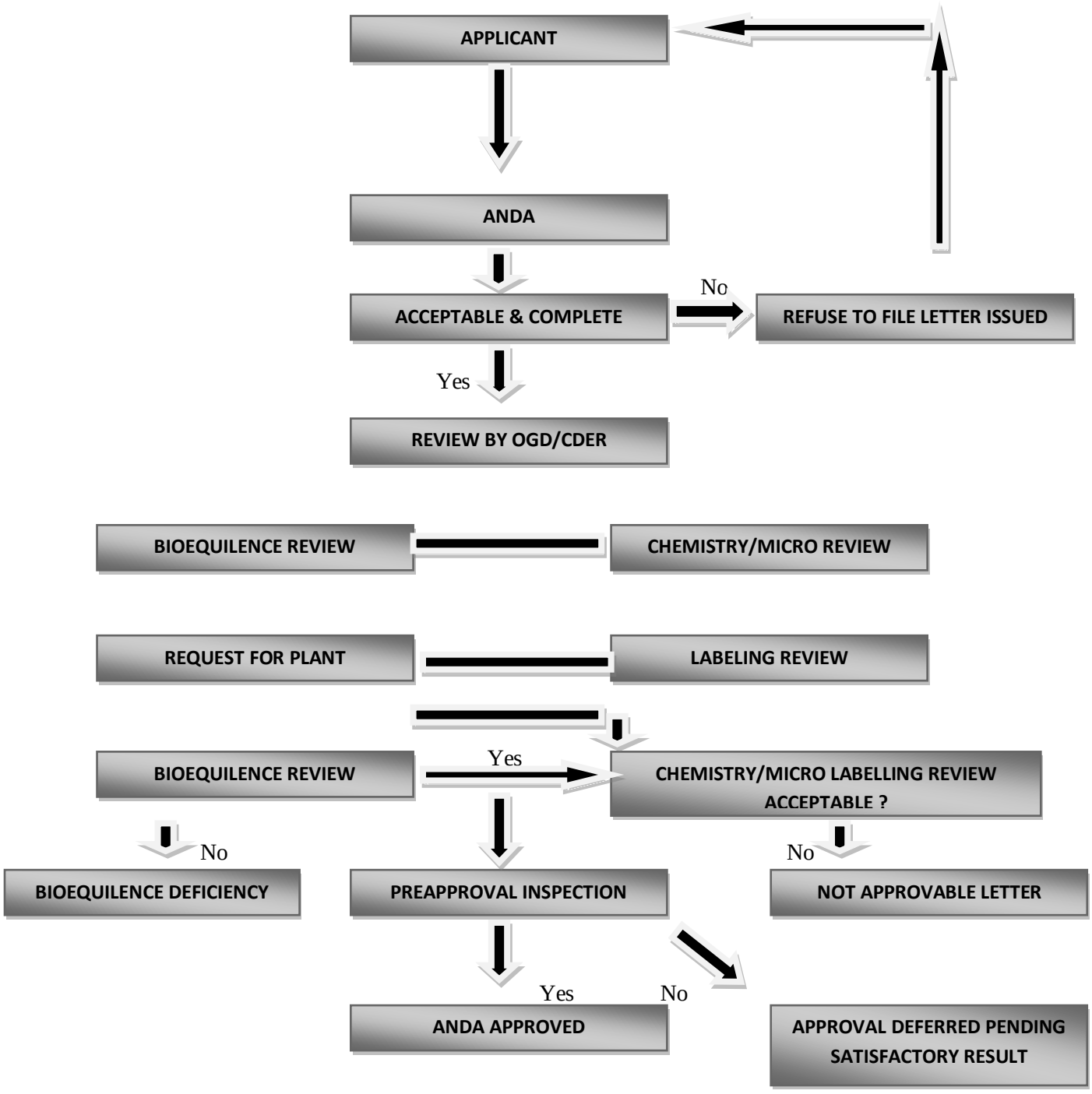


Figure 4: Generic Drug Approval (ANDA Approval) [6]

Europe

Similar to the US requirements, there are two regulatory steps to go through before a drug is approved to be marketed in the European Union. These two steps are clinical trial application and marketing authorization application. There are 27 member states in the European Union (as of August 2007); Clinical Trial Applications are approved at the member state level, whereas marketing authorization applications are approved at both the member state and centralized levels.[7]

Centralized procedure- The centralized procedure is one which allows applicants to obtain a marketing authorization that is valid throughout the EU.[8]

- Results in a single authorization valid in EU, Norway, Iceland and Liechtenstein.
- Application evaluated by an assigned Rapporteur.
- Timeline: EMA opinion issued within 210 days, and submitted to European Commission for final approval.

Centralized process is compulsory for:

- Those medicines which are derived from any biotechnology processes, such as genetic engineering.
- Those medicines which are intended for the treatment of Cancer, HIV/Aids, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions.
- Medicines officially designated 'orphan medicines'(medicines used for rare diseases).

Mutual Recognition Procedure

The Mutual Recognition procedure allows applicants to obtain a marketing authorization in the member states(Concerned Member State) other than the member state (Reference Member State) where the drug is previouslyapproved.[9]

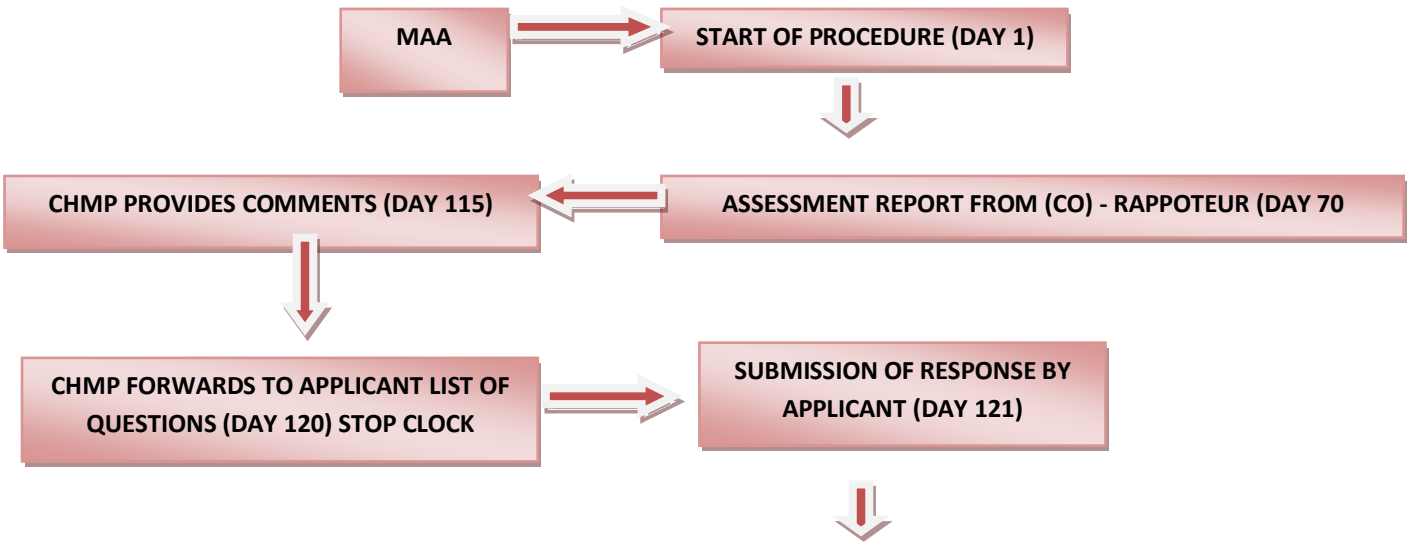
- Applicant submits identical dossier to all EU member states in which it wants authorization, including required information.
- As soon as one Member State decides to evaluate the medicinal product (at which point it becomes the "RMS"), it notifies this decision to other Member States (which then become the "CMS"), to whom applications have also been submitted.
- RMS issues a report to other states on its own findings.
- Generic industry is the major user of this type of drug approval procedure.
- This process may consume a time period of 390 days.

Nationalized Procedure the Nationalized procedure is one which allows applicants to obtain a marketing authorization in one member state only.[10, 11]

In order to obtain a national marketing authorization, an application must be submitted to the competent authority of the Member State.

- New active substances which are not mandatory under Centralized procedure can obtain marketing authorization under this procedure.
- Timeline for this procedure is 210 Days

The regulatory approval Centralized Mutual recognition procedure In Europe is outlined in Figures 5& 6.



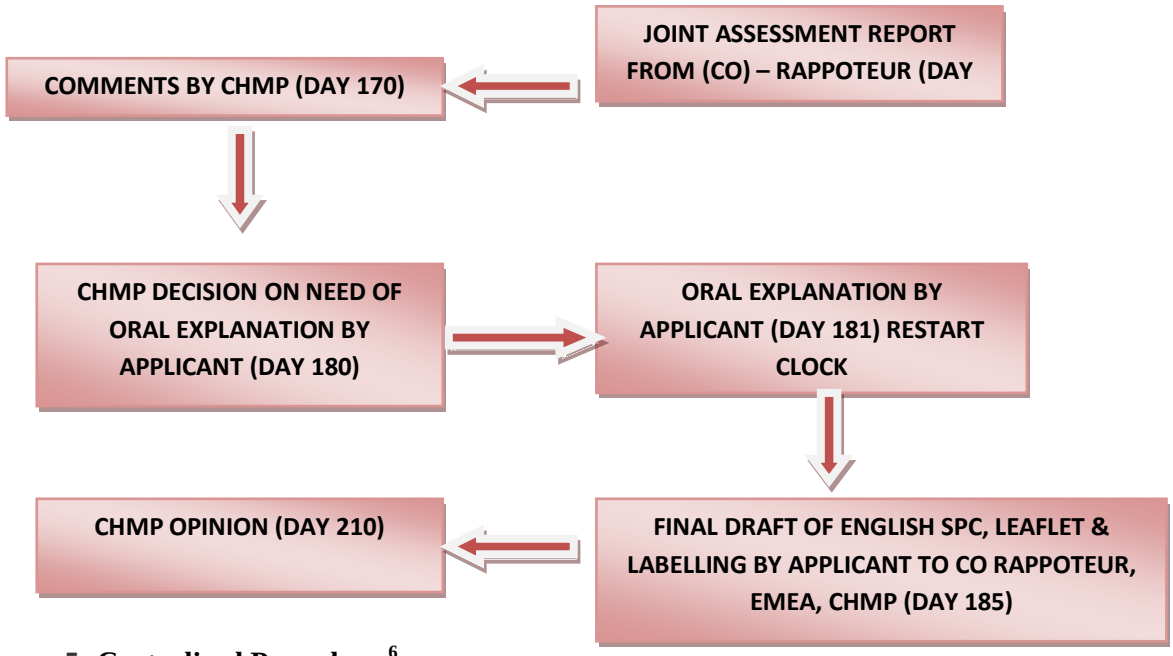


Figure 5: Centralized Procedure [6]

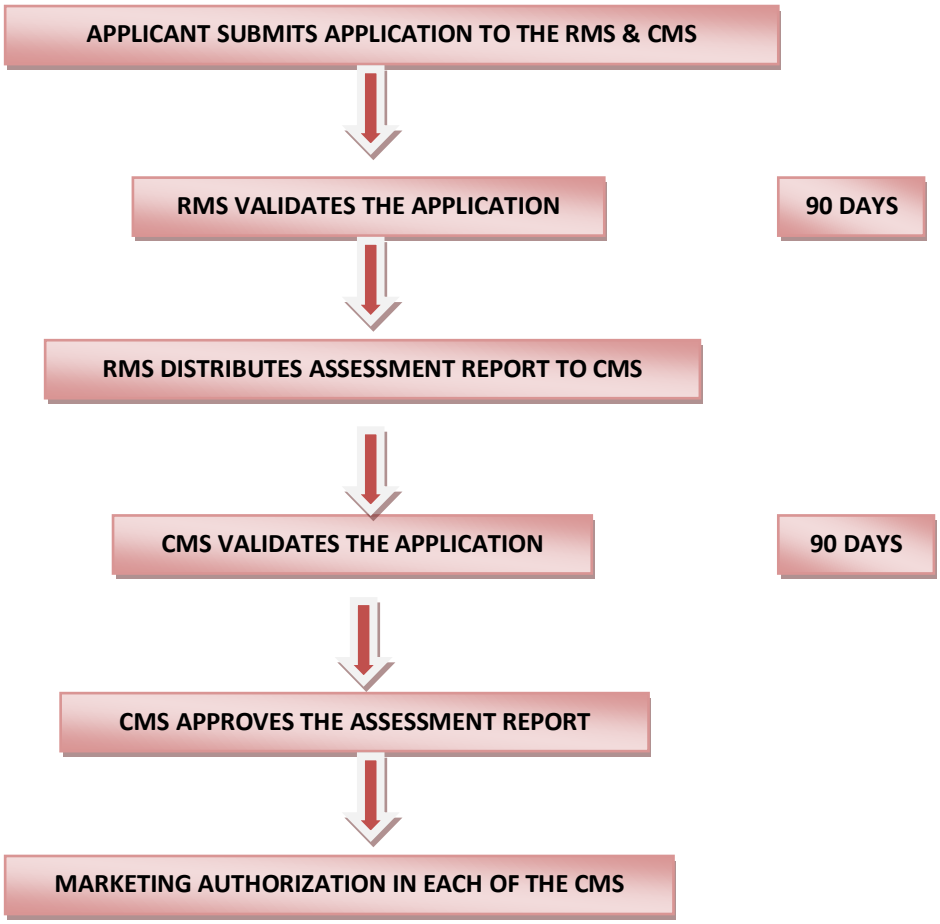


Figure 6: Mutual Recognition Procedure [6]

Decentralized procedure

Using this procedure, companies may apply for authorization simultaneously in more than one EU country for products that have not yet been authorized in any Upcountry and essentially do not fall within the centralized procedure's essential drugs list.[12, 13] Based on the assessment report which is prepared by theRMS& any comments made by the CMS, MA should be granted in accordance with the decision taken by theRMS&CMS in this decentralized procedure.

- Generally used for those products that has not yet received any authorization in an EU country.
- Time: 210 days.

The regulatory approval Decentralized procedure In Europe is outlined in Figure 7.

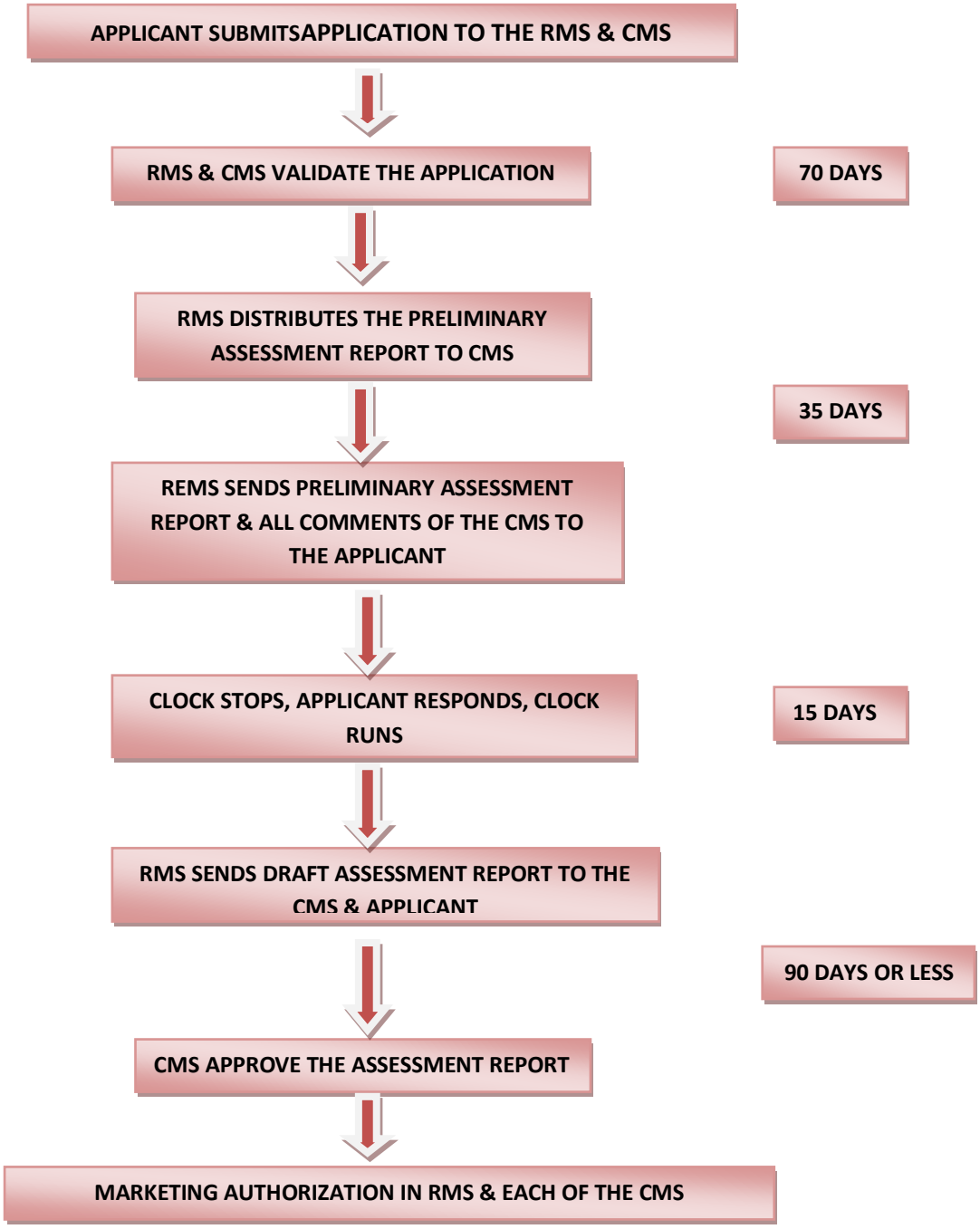


Figure 7: Decentralized Procedure [6]

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 labeled 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 pecific 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.1 Bioequivalence studies usually involve a comparative study of the product in human volunteers, but bench top 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.

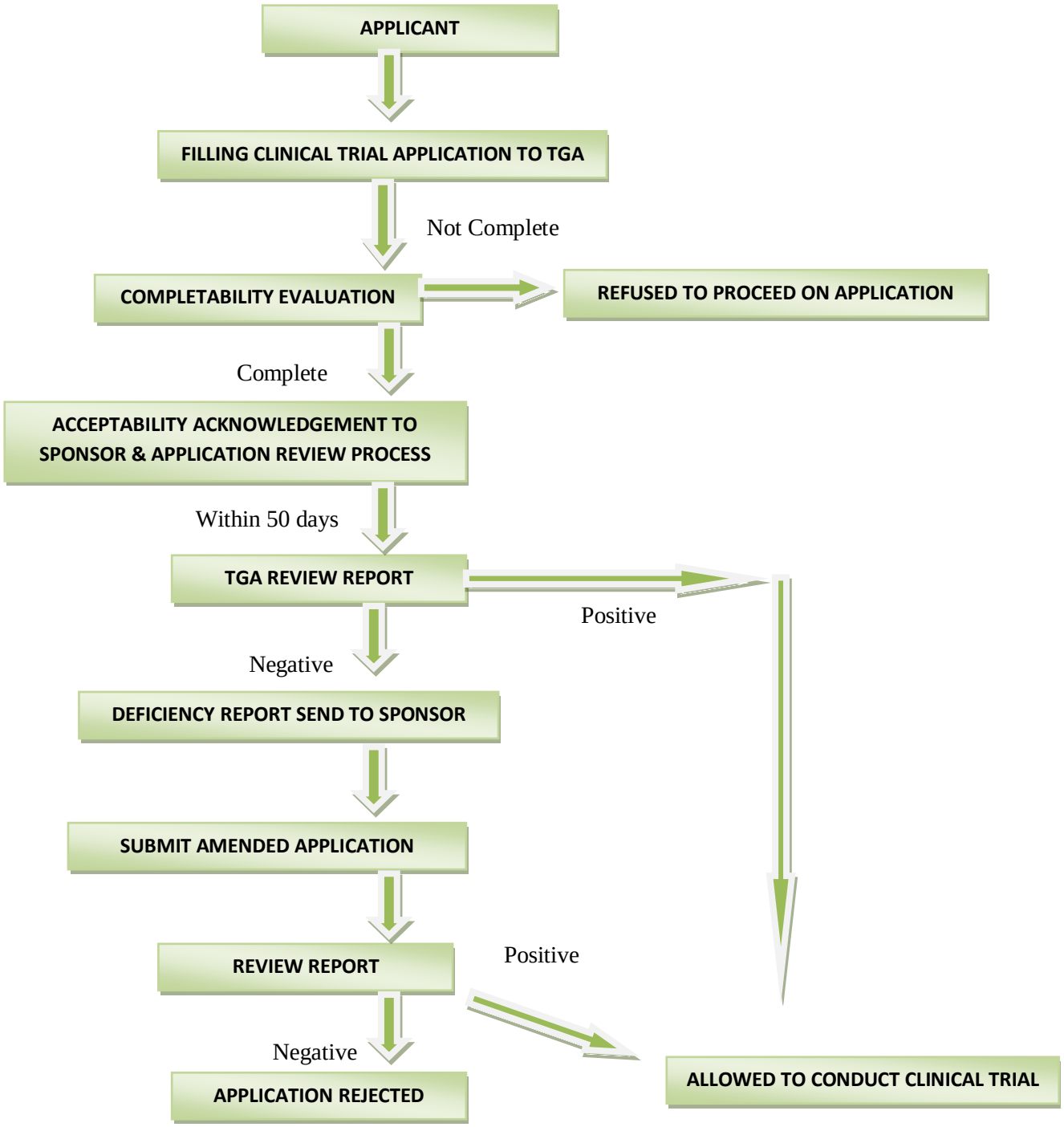


Figure 8: Clinical Trial Authorization Process of Australia under CTX Scheme[5]

The clinical trial approval and regulatory approval procedure In Australia is outlined in Figures 8&9 respectively.

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.3 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.3 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[4]

NDA-New Drug Application, DSEB-Drug Safety and Evaluation Branch, TGA-Therapeutic Goods Administration, ADEC-Australian Drug Evaluation Committee.

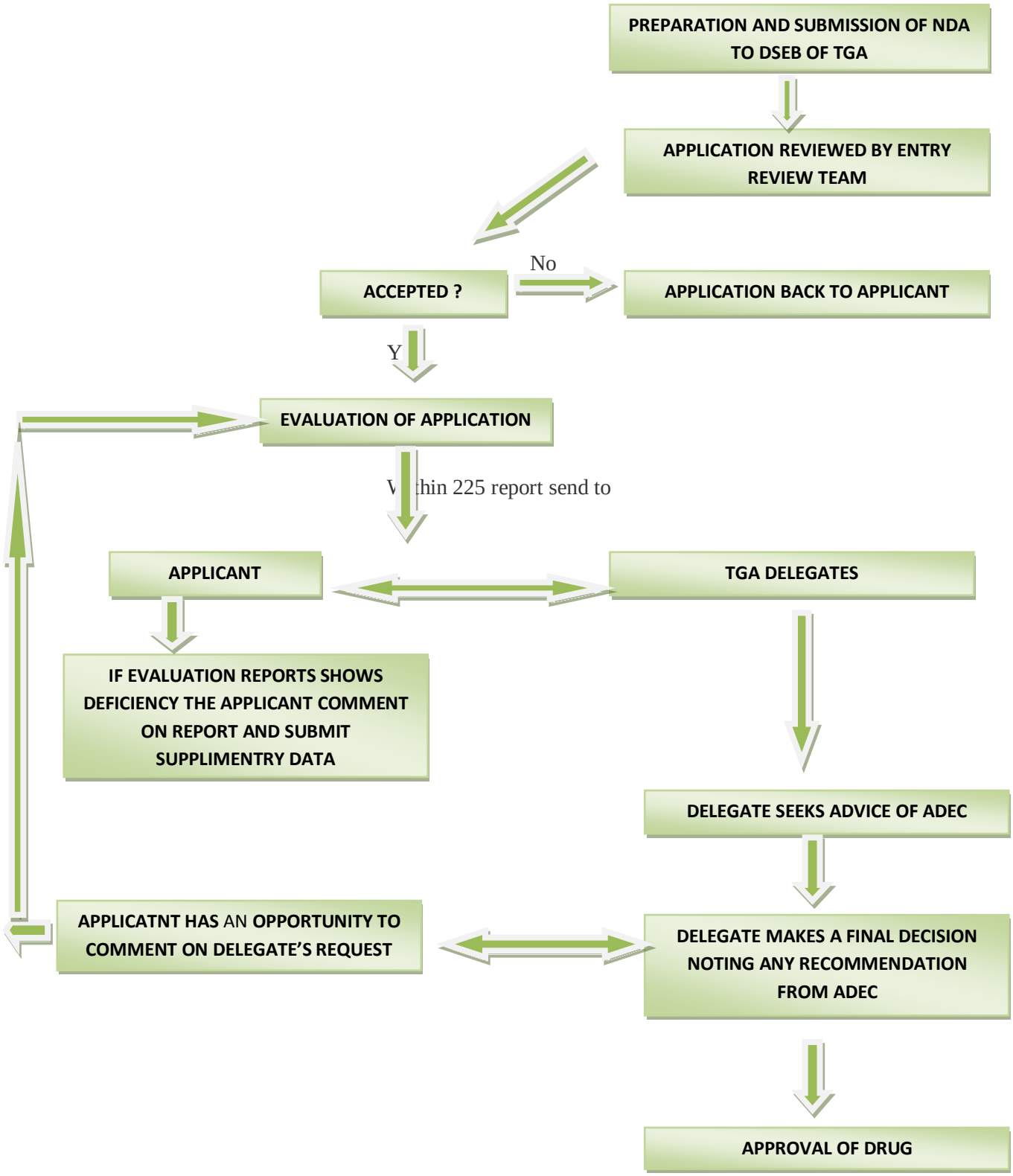


Figure 9: New Drug Registration Process of Australia [5]

China

In 1963, for the management of new drugs, Chinese Ministry of Health planned drug regulation. The China's State Pharmaceutical Administration in collaboration with Ministry of Health, in 1979, published the New Drug Management Regulations (no need to conduct systematic scientific experiments on new drugs). In view of protecting the public health and promoting the economic developments in pharmaceuticals, the first comprehensive Drug Administrative Law was framed in 1985. This law was amended in 1999 by two additional provisions for new drug approval and provisions for new biological product approval. The approval process of New Drug Applications (NDA) includes sufficient preclinical data for verification of drug's safety and justification of the commencement of clinical trials. The Drug Administrative Law was further revised in 2001 requiring premarket testing, approval for new drug products, and prohibits drug adulteration[14].

The Drug Administrative Law authorizes the State Food and Drug Administration (SFDA) to approve new drugs for marketing. The new drug registration process also consists of the clinical study application and the new drug application. The Provincial Drug Administration Authorities (PDAAs) should organize the works of the formal review of submitted materials i.e. on-site examination and sampling just after receiving the drug registration application. The aim behind the formal review is to guarantee the content and format of the submitted materials is in line with the requirements and all the required materials have been submitted. After formal review, the PDAAs send the qualified applications to the SFDA for further review. The import drug registration application should be directly submitted to SFDA by the applicant. SFDA's Department of Drug Registration carefully reviews the completeness of the submitted materials, files the qualified applications and transmits all the materials of qualified applications to the Center for Drug Evaluation (CDE) directly attracted to SFDA. CDE determine whether the safety and effectiveness information submitted for a new drug are adequate for manufacturing and marketing approval and send the report of review to SFDA. SFDA Carefully consider the recommendations and review results of CDE and makes a decision whether or not the drug registration application can be approved and issues the certificate of drug approval and drug approval number to the qualified applicant. Figure 10and 11 represents the clinical trial approval process and new drug approval process of China, respectively[5, 14, 15.]

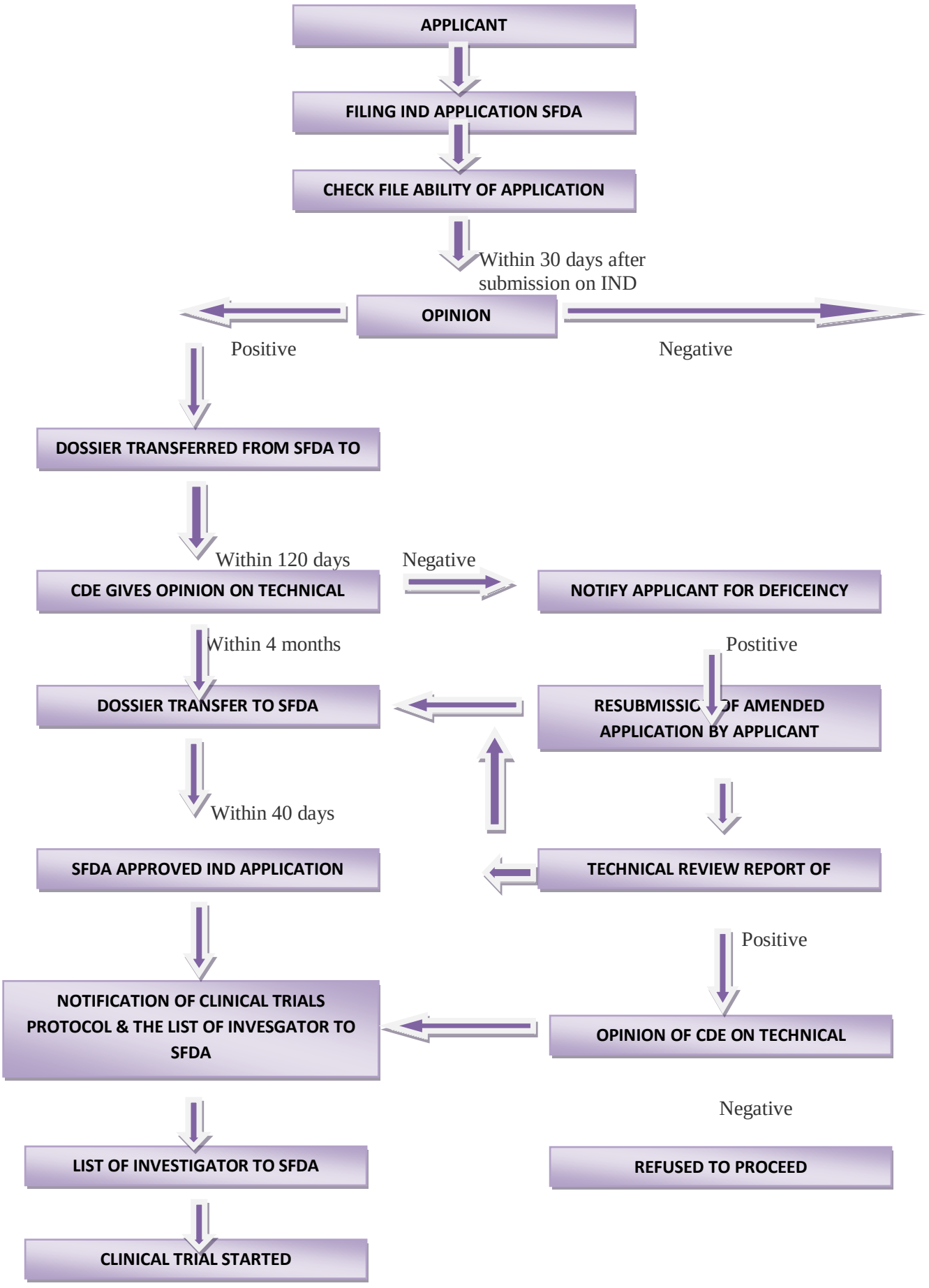


Figure 10: Clinical Trial Application Approval Process of China[5]

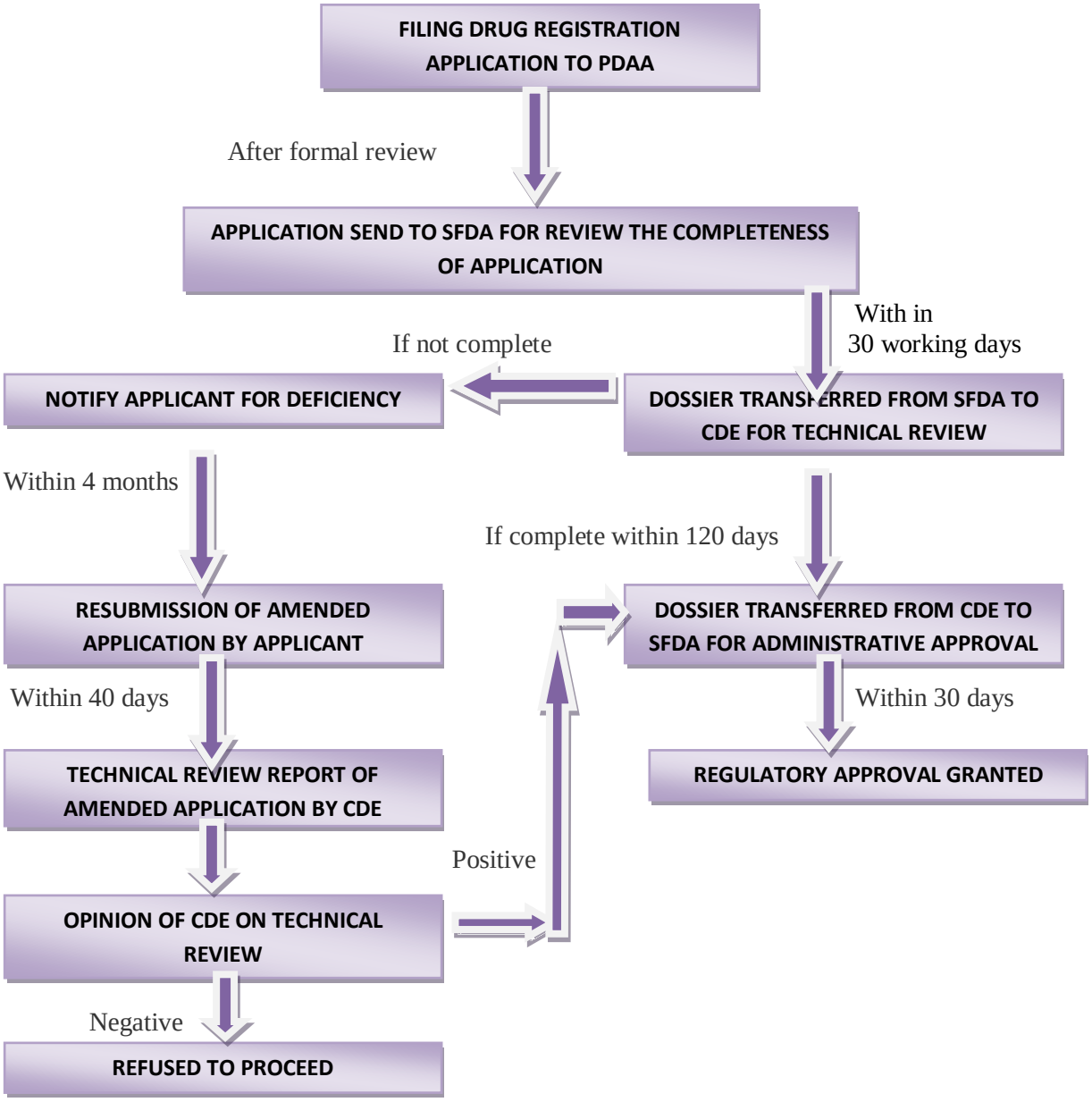


Figure 11: New Drug Registration Process of China[5]

Turkey:

In Turkey, the Ministry of Health, General Directorate of Pharmaceuticals and Pharmacies is the sole authority in charge of registration, marketing approval/authorization, pricing of pharmaceuticals, legal classification and inspection. The role of this authority is to provide for registration, marketing approval/authorization and pricing of pharmaceutical products, to define rules to be followed as well as to control the advertisement of pharmaceutical products, to undertake inspection of pharmaceutical products and pharmaceutical production plants in Turkey. According to the World Health Organization, Turkey's drug licensing standards closely resemble the countries of the European Union. In Turkey, regulatory approval procedures of human medicinal products are conducted in accordance with the "Registration Regulation of Human Medicinal Products," published for effect in Official Gazette #25705 of 19.01.2005. The objective of the Registration Regulation of Human Medicinal Products is to set forth the principles, procedures, and policies regarding registered human medicinal products, with a view to achieving the desired efficacy and safety as well as the required quality in medicinal products for human use. In Turkey, new drugs are granted marketing authorization after reviewing their safety, efficacy and quality. The General Directorate of Pharmaceuticals and Pharmacy (İEGM) is charged with the marketing authorization process, and is the principal national authority for approval, pricing, legal classification and inspection of drugs. The General Directorate is supported by scientific committees in conducting medical, pharmaceutical and clinical evaluations of products proposed for

approval. Committees evaluate documents submitted by pharmaceutical manufacturers, and their decisions provide the basis for marketing authorization and licensure. The application is initially reviewed by the Advisory Committee for Registration of Human MedicinalProducts, usually taking 3 to 4 months. The third step in the marketing authorization processinvolves setting the product price, which is the responsibility of İEGM Pricing Branch. Thus, pricing is apart of the regulatory approval process. The price is set using an external reference price chart. The pricing procedure usually takes 3 to 6 months. After completion of pricing negotiations, the committee reviews the application for bioequivalence (for generic products) and bioavailability (for original products). For alignment with the European Union regulations, the Registration Regulation of Human Medicinal Products requires following the Common Technical Document (CTD) guidelines for preparing the marketing authorization application file. Accordingly, the CTD guidelines were issued by the Ministry of Health, and marketing authorization applications are accepted in CTF format since 30.12.2005.

The General Directorate of Pharmaceuticals and Pharmacy was the sole authority charged with granting marketing authorization and selling permits for, and pricing, classifying and reviewing drugs in Turkey. By "Decree Law #633 on the Organization and Mandate of the Ministry of Health and Subordinate Agencies – KHK/663," published in Official Gazette #28103, second edition, of 02.11.2011, however, a "Medicines and Medical Devices Agency of Turkey" was established, with a private budget and having the status of a public juristic person, as a subordinate organ of the Ministry of Health, charged with overseeing and regulating matters pertinent to medicines, active ingredients and recipients used in the production of medicines, substances subject to national or international control, medical devices, in vitro diagnostic medical devices, traditional herbal medicinal products, cosmetics, homeopathic medicinal products and special-purpose dietary goods in line with Ministry policies and objectives.

According to the Registration Regulation of Human Medicinal Products, the Ministry conducts a preliminary review to evaluate whether the marketing authorization application file is complete and free from any omissions in terms of the requisite data and documents which must be submitted, depending on the type of application and applicable requirements laid down in the Registration Regulation of Human Medicinal Products. The Ministry completes the administrative review and notifies its outcome to the applicant within 30 (thirty) days after receipt of the application file at the Ministry. In the event that deficiencies are identified, the applicant has 30 (thirty) days to address such deficiencies. The second preliminary review, conducted after omissions have been addressed and resubmitted to the Ministry, is completed also within 30 (thirty) days. In the event that Ministry's preliminary review finds the applicant to be lacking the requisite qualifications prescribed in the Registration Regulation of Human Medicinal Products, or the file submitted for second preliminary review is again found to be marred by omissions, the application is rejected and returned to the applicant. According to the Registration Regulation of Human Medicinal Products, the Ministry must complete its regulatory review of the file within 210 (two hundred and ten)days, provided the application file is free from any omissions and has cleared through the preliminary review according to the Registration Regulation of Human Medicinal Products. However, the clock stops for the duration of any extraordinary circumstances or until the applicant submits any data or documents requested by the Ministry, which do not count toward the 210-day timeframe. The Registration Regulation of Human Medicinal Products lists the following product-related criteria for granting marketing authorization to a human medicinal product: the efficacy of the product has been proven under its intended conditions of use, the safety of the product has been proven, and the product has the appropriate technical and pharmaceutical characteristics. The Ministry may, however, waive some of these criteria taking account of pharmacoeconomic data, when public health considerations warrant it. Marketing authorization is granted to products which, according to data and documents submitted to and reviewed and analyzed by the Ministry, fulfill the requirements of the Registration Regulation of Human Medicinal Products. Before offering a product for sale for the first time after receipt of marketing authorization, product samples representative of the final commercial product must be submitted to the Ministry to obtain a "selling permit." The Ministry reviews the samples for conformity of the package leaflet, package and label information, and price, and grants a selling permit if the product meets the requirements. In view of the above procedural details, the regulatory approval procedure in Turkey is outlined in Figure. 12

APPLY FOR GMP INSPECTION AND OBTAIN GMP CERTIFICATE FOR IMPORTED MEDICINES

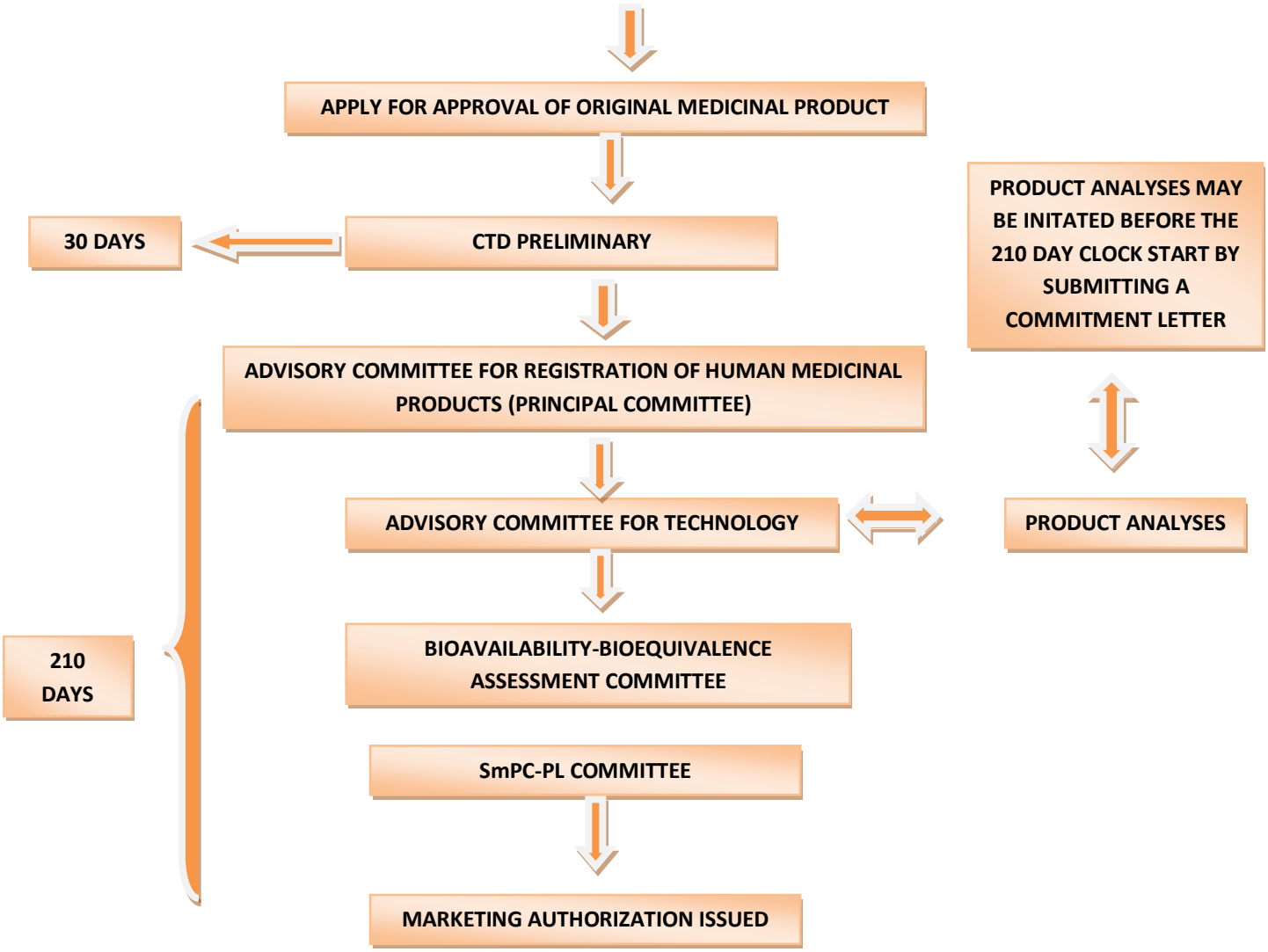


Figure 12: Overview of the Regulatory Approval Procedure in Turkey [16]

Canada:

Health Canada's Therapeutic Products Directorate (TPD)regulates pharmaceutical drugs (prescription and nonprescription) and medical devices for human use. Health Canada's Biologics and Genetic Therapies Directorate (BGTD) is responsible for regulating biologics ,including blood and blood products, viral and bacterial vaccines, cells, tissues, organs and xenografts. Canada's systems for regulating drug products are verysimilar to those in the United States. At the federal level, the Therapeutic Products Directorate, an agency of Health Canada that regulates Canada's drug supply, is Canada's counterpart to the FDA. All drug products sold in Canada must be approved by the Therapeutic Products Directorate. Pharmacies in Canada are regulated by the provinces; a similar system to the U.S. in which states regulate pharmacies.

The Canadian pharmaceutical market is the eighth largest in the world, accounting for about two percent of theworld market by sales. Canada also has the fourth fastest growing pharmaceutical industry after China, the US and Spain and has shown a steady growth trend. New drug submission required for new drugs that have not been sold in Canada for a sufficient time and insufficient quantity to establish their safety and effectiveness—includes clinical trial information and details on production, packaging, labelling, conditions for use, and side effects. When an NDS is submitted to TPD, it first undergoes an administrative screening procedure to ensure that all necessary parts are included and in the required format. This is not a review of the data. The goal is to complete the screening procedure within 45 days of receipt of thins. The file is then directed

toward the appropriate Bureau responsible for reviewing drugs in a given therapeutic area. TPD currently has a 300-dayperformance guideline to complete a standard NDS review, and 180 days to complete a priority NDS.

Terms:

Notice of Deficiency (NOD): the review cannot continue due to deficiencies or significant omissions in the file.

Notice of Deficiency: Withdrawal (NOD/w): if the response to an NOD is inadequate, the TPD will issue a NOD/w letter, indicating the company must withdraw the submission.

Notice of Non-compliance (NON): indicates the review is complete and the submission is deficient or incomplete. It is usually not as severe as an NOD.

Notice of Non-compliance: Withdrawal (NON/w): if the response to a NON is inadequate, the company must withdraw the submission.

Notice of Compliance (NOC): once all issues have been resolved, the TPD will issue an NOC. If Health Canada is not satisfied that all issues have been satisfied, the TPD will issue either an NOD/w or NON/w.

Priority Review: A review status granting eligible new drug submissions and supplements to new drug submissions a shortened review target. This status is granted following review and approval of a request submitted by the sponsor of the drug.

Pre submissions:

- It familiarizes reviewers with the product.
- It identifies the studies on which the sponsor is relying to establish the effectiveness of the drug.
- It provides an opportunity for the sponsor to discuss the submission with Health Canada and obtain feedback.
- Regarding areas of concern or the potential for priority review.

- Meeting requests
- Pre-submission Packages:

Pre-NDS/SNDS meetings:

- A cover letter
- An agenda for the meeting
- A list of specific issues (grouped by discipline) the sponsor would like to discuss or have addressed
- A brief summary of the drug product for which the meeting is being called proposed strengths and dosages
- An overview of the market history of the product including the foreign regulatory status of the drug etc.

Submission filing:

A sponsor files duplicate copies of its submission to the TPD, at which point it undergoes a screening procedure.• Sponsors seeking a priority review or review under the NOC/c (Notice of Compliance with conditions) regulations should submit a request in advance of filing the NDS.• For a priority review request, a response from the TPDshould be received within 30 calendar days.• Submission Holds:

- SIPD/CR Holds
- Switch Hold
- Cost-recovery Hold
- Regulatory Hold

Screening:

- The TPD will undertake a screening process to ensure itis complete and in the appropriate format.
- This is an administrative review and does not include any technical review of the information.
- The TPD targets 45 calendar days to complete the screening of an NDSs, SNDSs, ANDSs, SANDSs,

- Once the screening is complete and accepted, the submission enters the queue for technical review.
- If the screening process identifies deficiencies in theNDS, the sponsor will receive a screening deficiency notice, and has 45 calendar days to respond and resolve any identified deficiencies.

Evaluation of Submissions

The TPD has a target of 300 calendar days to complete its evaluation.

- Update Notices
- Requests for Clarification During Screening or Review of the Submission - all submission types
- Notices of Deficiency (NOD) - NDSs, SNDSs, ANDSs, SANDSs, DINAs Notices of Noncompliance (NON) - NDSs, SNDSs, SNDSC, ANDSs, SANDSs, DINAs

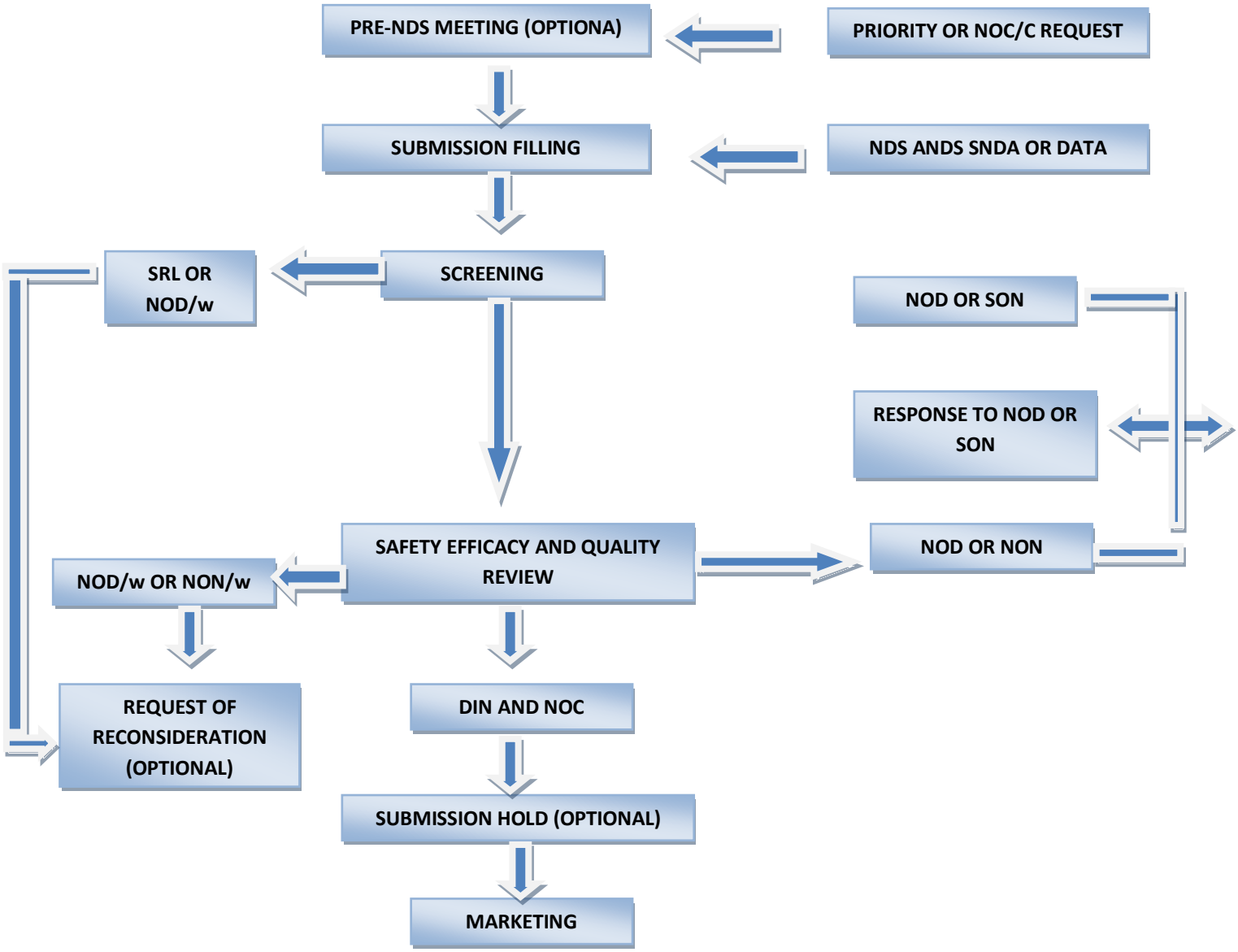


Figure 13: Overview of the Regulatory Approval Procedure in Canada[16]

Reviewer reports:

The reviewer reports will be provided to the sponsor within seven calendar days following the issuance of an NOD, an NOD/w, an NON or an NON/w. Sponsors may request a reviewer's report following the

Issuance of an NOC, and it is supposed to be provided within 30 calendar days The regulatory approval procedure in Canada is outlined in Figure. 13.

Conclusion

The new drug approval processes of various countries similar and differ in some aspects. Applicant firstly files an application to carry out clinical trial, and only after the approval by the regulatory authority, the applicant conducts the clinical studies and further submits an application to the regulatory authority for marketing authorization of drug. In all countries, information submitted to regulatory authorities regarding the quality, safety and efficacy of drug is similar; however, the time, fee and review process of clinical trials and marketing authorization application differs. For the purpose of harmonisation, the International Conference on Harmonisation (ICH) has taken major steps for recommendations in the uniform interpretation and application of technical guidelines and requirements. This step will ultimately reduce the need to duplicate work carried out during the research and development of new drugs. Therefore, harmonization of drug approval processes either by ICH or WHO may be initiated at global level.

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