

DRUG APPROVAL PROCESSES IN PHARMACEUTICAL MARKET

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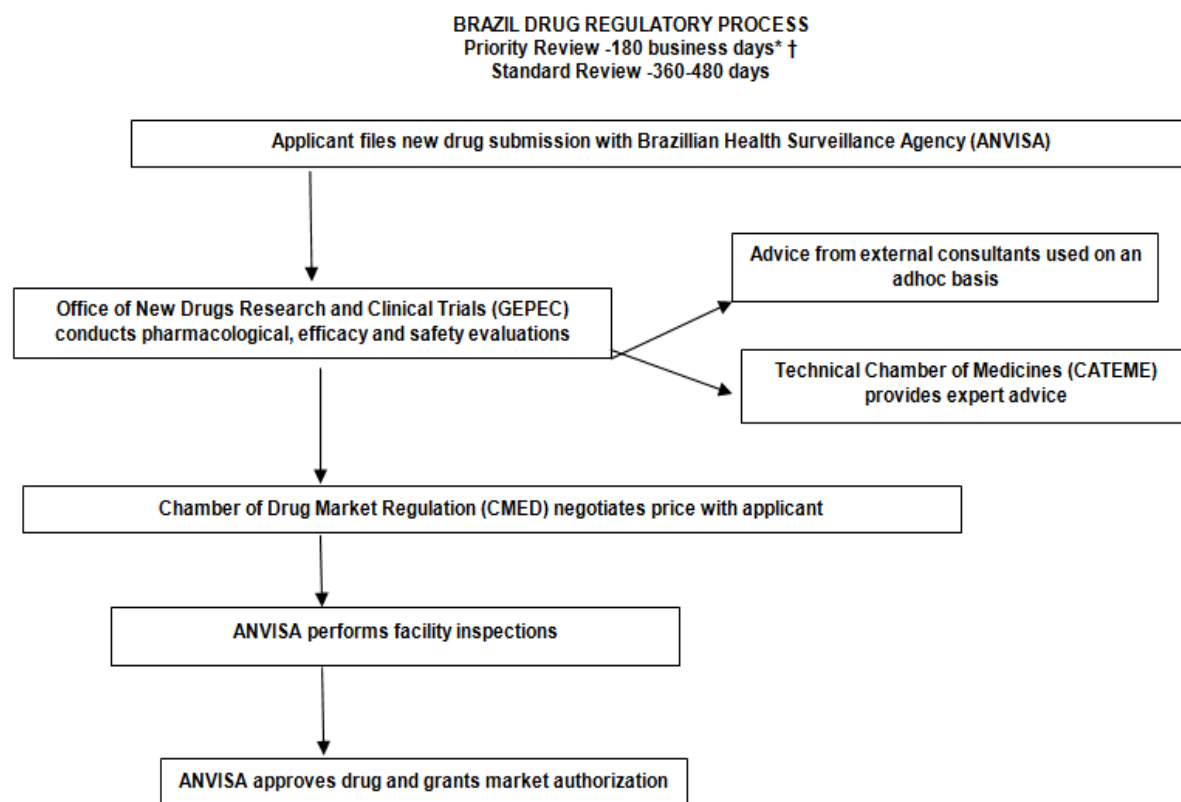
ABSTRACT

In the developing world developing new drugs requires great research. In view of protecting the public health and promoting the economic developments in pharmaceuticals, the first comprehensive drug administration law was formed in 1985. This law was amended in 1999 by two additional provisions for new drug approval and provisions for new biological product approval. Approval new drug products was prohibiting drug adulteration. Based on these views in different countries different regulatory bodies were emerged and frame the different rules and regulations. Now this article detailed about formal process in the pharmaceutical market of some countries (Australia, Brazil, Canada, China, India, Japan, Saudi Arabia, South Africa).

Keywords: Drug approval, Drug administrative law, Pharmaceutical Market, Provisions.

DRUG APPROVAL PROCESS IN BRAZIL¹

The regulatory authority of Brazil is Brazilian Health Surveillance Agency (ANVISA). In this drug approval process priority review takes 180 business days and standard review takes 360 – 480 days. Applicant may be a company or representative of company initially files a new drug application to the Brazilian health surveillance agency ANVISA. The office of new drugs research and clinical trials (GEPEC) conducts pharmacological, efficacy and safety evaluations. It takes advice from external consultants used on an adhoc basis and from Technical Chamber of Medicines (CATEME). Based on the advices and all the evaluations submits a report to the chamber of Drug Market Regulation (CMED) which negotiates price with applicant and fixes a particular price limit. Then ANVISA performs facility inspections and upon all the criterion satisfaction it approves the drug and market authorization is granted.



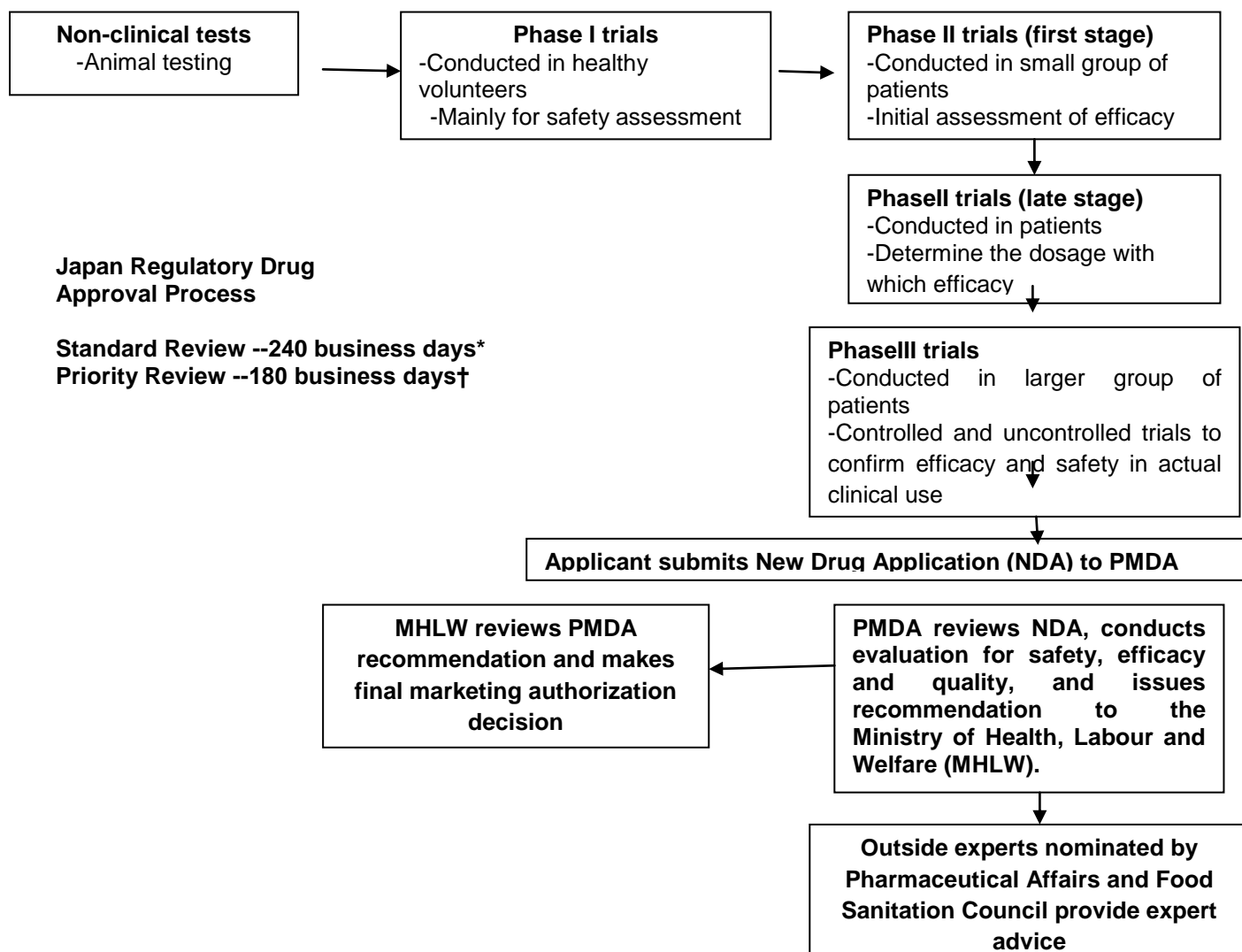
DRUG APPROVAL PROCESS IN JAPAN²

The regulatory authority of Japan is ministry of Health, Labour and Welfare (MHLW). In this drug approval process priority review takes 180 business days and standard review takes 240 business days.

Pharmaceuticals and Medical devices Agency (PMDA) phases from clinical trials to New Drug Application

Pre-clinical and clinical timelines vary depending on the type of drugs, clinical results etc. Pharmaceuticals and Medical Devices Agency (PMDA) Phases from clinical trials to New Drug Application. Non clinical testing involves animal testing followed by Phase I trials where tests are conducted in healthy volunteers for safety assessment. Phase II trials in the first stage is conducted in a small group of patients where initial assessment of efficacy is performed and in the last stage the dosage with which efficacy in patients is determined.

The Phase III trials are conducted in larger group of patients where controlled and uncontrolled trials to confirm efficacy and safety in actual clinical use. Then applicant submits New Drug Application (NDA) to PMDA. It reviews NDA, conducts evaluation for safety, efficacy and quality, and issues recommendation to the Ministry of Health, Labour and Welfare (MHLW) Outside experts nominated by Pharmaceutical Affairs and Food Sanitation Council provide expert advice and MHLW reviews PMDA recommendation and makes final marketing authorization decision.

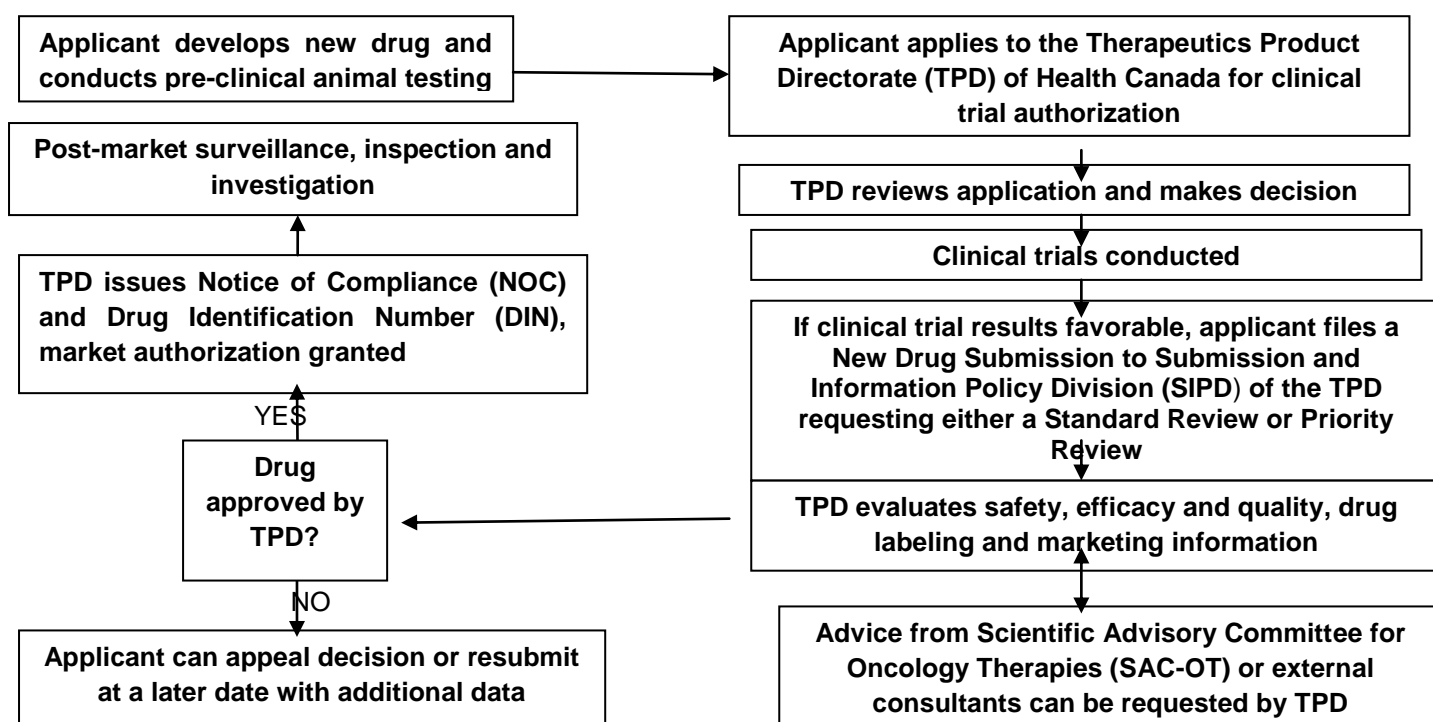


DRUG APPROVAL PROCESS IN CANADA^{3,4}

The regulatory authority of Canada is Health Canada. In this drug approval process priority review takes 180 business days and standard review takes 360 business days.

Applicant develops new drug and conducts pre-clinical animal testing. Then applicant applies to Therapeutics Product Directorate (TPD) of Health Canada for clinical trial authorization. TPD reviews application and makes decision. Upon approval Clinical trials are conducted and if results are favorable applicant files a New Drug Submission to Submission and Information Policy Division (SIPD) of the TPD requesting either a Standard review or Priority review. TPD evaluates safety, efficacy and quality, drug labeling and marketing information and takes advice from Scientific Advisory Committee for Oncology Therapies (SAC-OT) or external consultants can be requested by TPD.

If the drug is not approved by TPD applicant can appeal decision or resubmit at a later date with additional data. If drug is approved then TPD issues Notice of Compliance NOC and Drug Identification Number DIN with granted market authorization.



Canada Regulatory Drug Approval Process
 Priority Review 180 business days
 Standard Review 360 business days

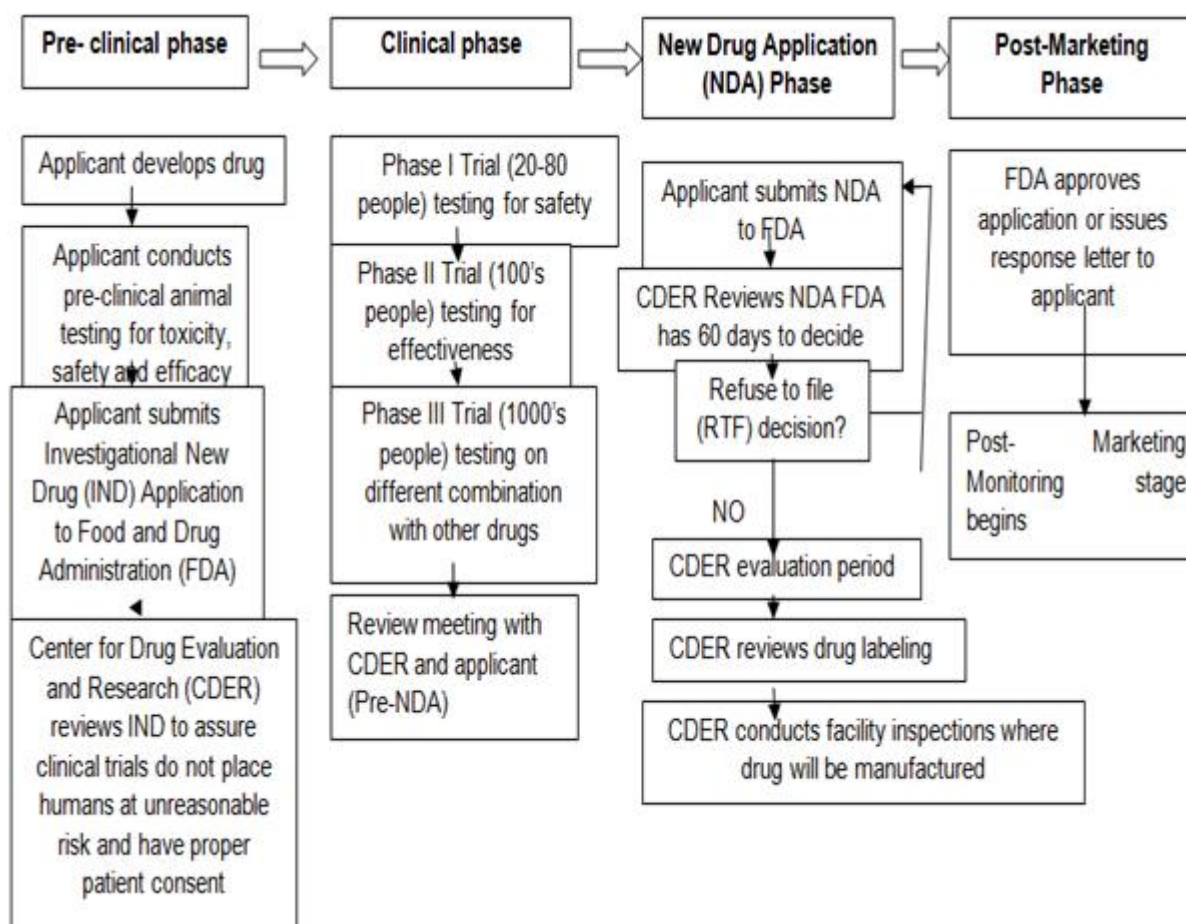
DRUG APPROVAL PROCESS IN UNITED STATES OF AMERICA [USA]⁵

The regulatory authority of USA is FDA Food and Drug Administration. In this drug approval process priority review takes 120-160 business days and standard review takes 200-240 business days.

In the Pre clinical phase the applicant develops the drug and conducts preclinical animal testing for toxicity, safety and efficacy and files IND to FDA. Center for Drug Evaluation and Research (CDER) reviews IND to assure clinical trials do not place humans at unreasonable risk and have proper patient consent.

In the Phase I Trial of clinical trials 20-80 people were tested for drug safety followed by Phase II Trial in 100's of people for drug effectiveness and in Phase III trial (1000's people) testing on different populations and combination with other drugs is performed and a Review meeting between CDER and applicant (pre-NDA) takes place.

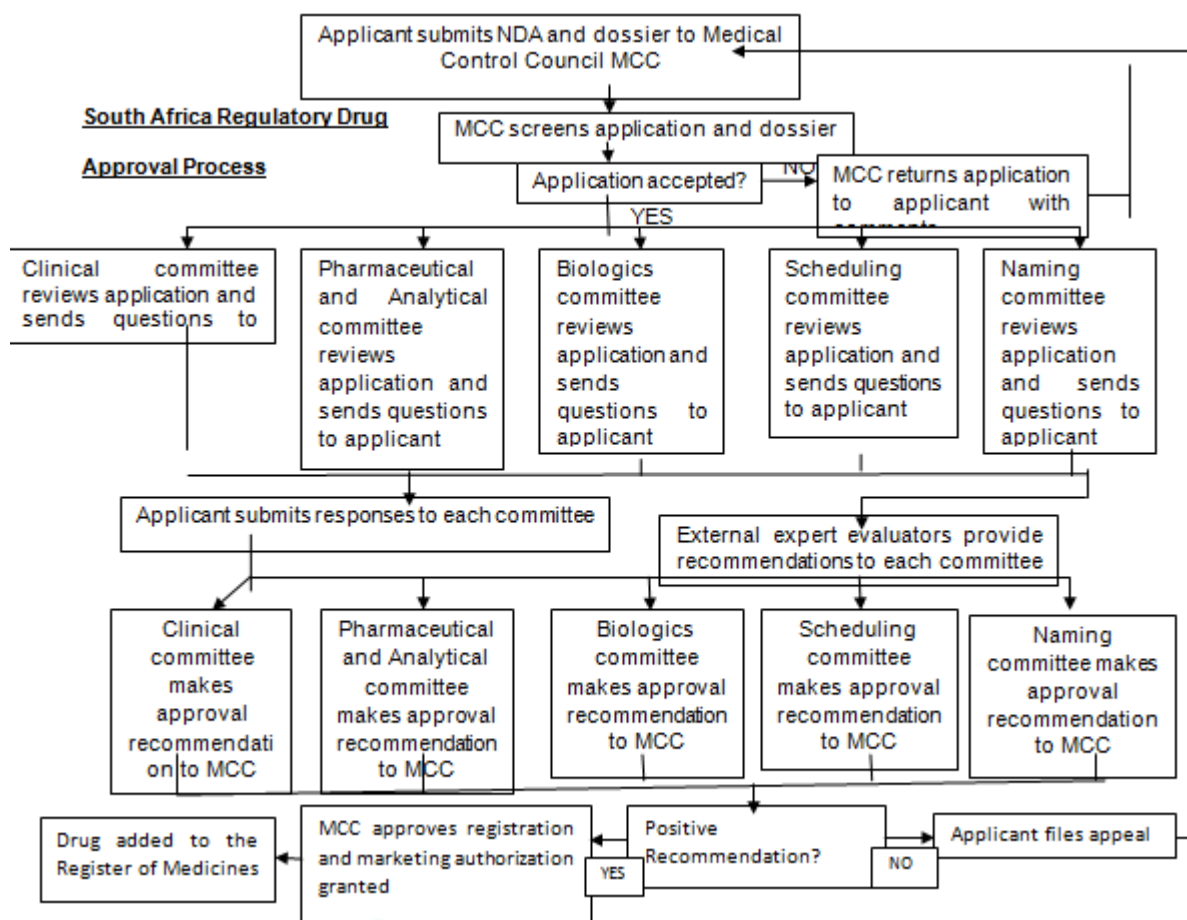
In the NDA phase the applicant submits an NDA to FDA where CDER reviews it and has 60 days to decide. If it doesn't refuse to file (RTF) decision then CDER evaluation period begins followed by drug labeling review and facility inspections where drug will be manufactured. When FDA approves application or issues response letter to applicant post-marketing monitoring stage begins.



United States of America Regulatory Drug Approval Process
Priority Review 120-160 business days*
Standard Review 200-240 business days†

DRUG APPROVAL PROCESS IN SOUTH AFRICA⁶

The regulatory authority of South Africa is MCC Medicines Control Council. In this drug approval fast track process takes 360-480 business days and standard process takes approx 720 business days. Applicant submits NDA and dossier to MCC which screens them and if the application is not accepted it returns the application to applicant with comments and if accepted then the application is forwarded to several committees where review of application is done and each committee sends questions to the applicant. Applicant submits responses to each committee and even external expert evaluators provide recommendations to each committee. Upon the data presented each and every committee makes approval and recommends to MCC. If the recommendation is positive then MCC approves registration and marketing authorization and drug added to the register of medicines if not applicant files appeal to MCC.

DRUG APPROVAL PROCESS IN AUSTRALIA ⁷

The regulatory authority of Australia is TGA Therapeutic Goods Administration. In this drug approval the standard process takes 240-260 business days.

In the initial Pre-submission phase (50 business days) applicant submits pre-submission planning form (PPF) to TGA 2-6 months before submission. TGA logs PPF and begins processing after first day of each month then it issues planning letter to applicant including submission milestones, any feedback and specific conditions.

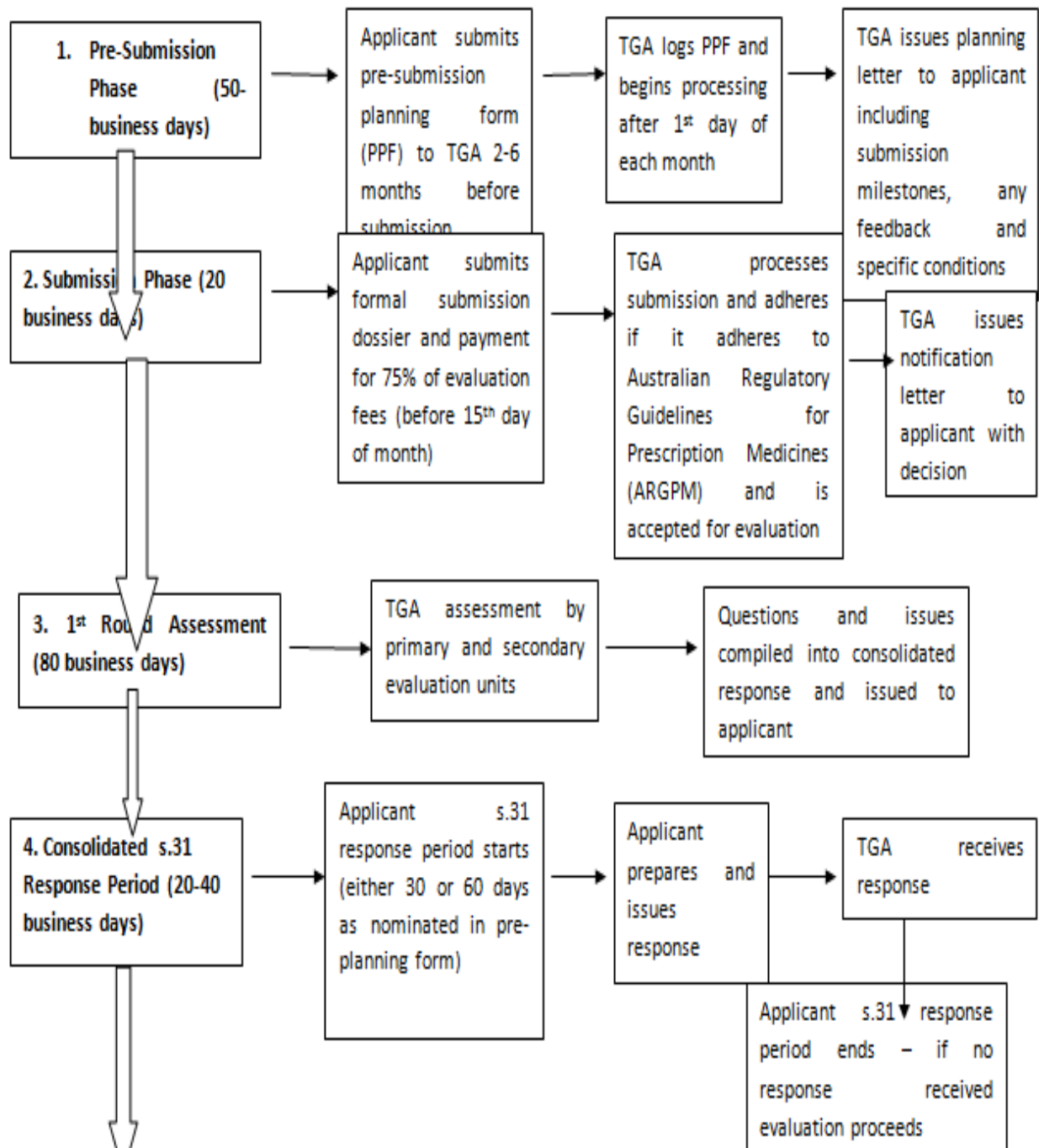
In the Submission phase (20 business days) applicant submits formal submission dossier and payment for 75% of evaluation fees before 15th day of month. TGA processes submission and determines if it adheres to Australian Regulatory Guidelines for Prescription Medicines (ARGPM) and is accepted for evaluation. TGA issues notification letter to applicant with decision.

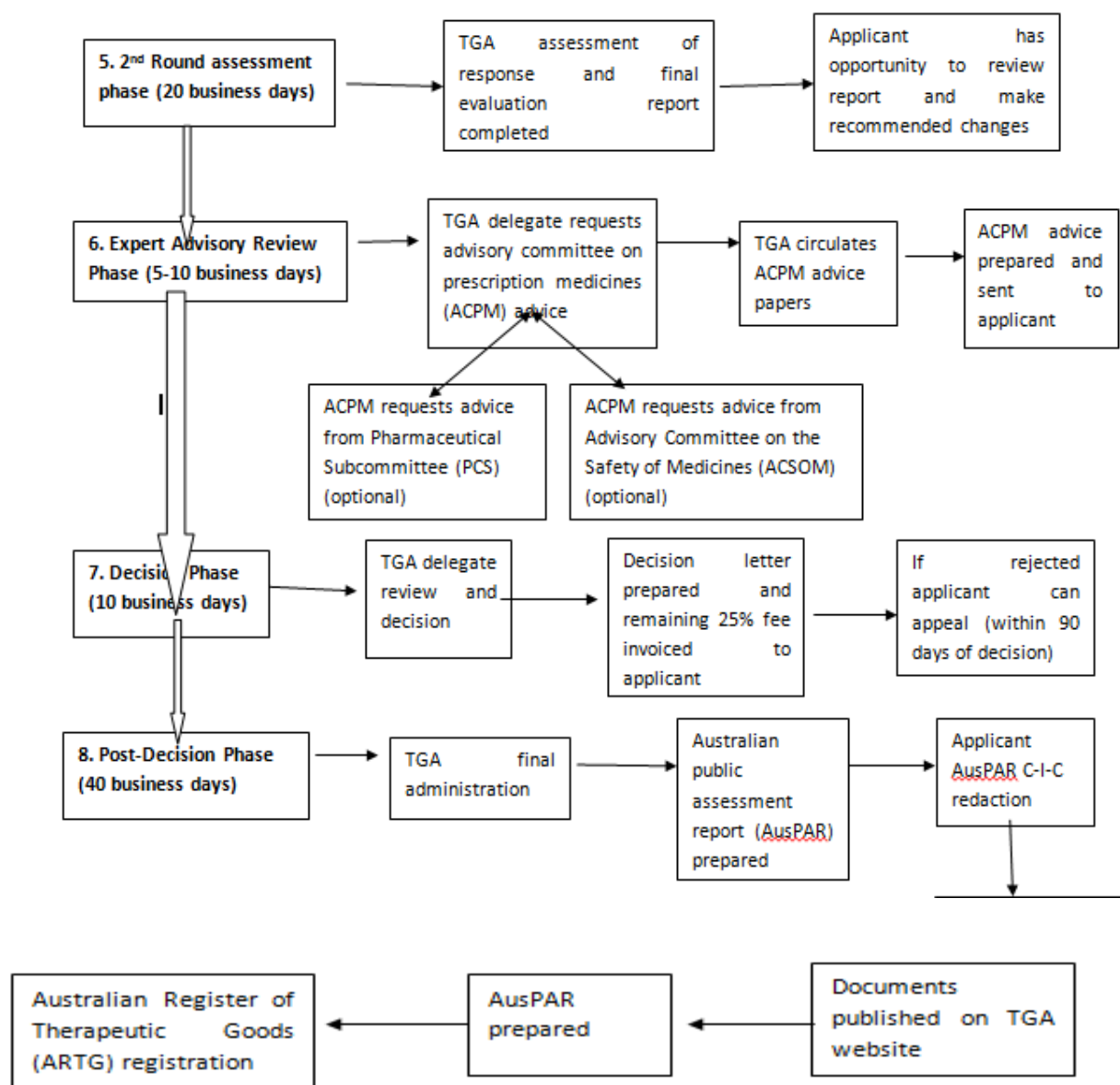
In the first round of assessment (80 business days) TGA assess by primary and secondary evaluation units and compiles questions and issues into consolidated response to the applicant. In the consolidated s.31 response period (20-40 business days) applicants.31 response period starts either 30 or 60 days nominated in PPF. Applicant prepares and issues response to TGA. Applicant s.31 response ends and if no response received evaluation proceeds.

In the second round assessment phase (20 business days) TGA assessment of response and final evaluation report completed and applicant has opportunity to review report and make recommended changes. It is followed by Expert advisory review phase (5-10 business days) where TGA delegate requests advisory committee on prescription medicines (ACPM) advice which in turn requests advice from Pharmaceutical subcommittee (PCS) and from advisory committee on the safety of medicines (ACSOM) which is optional. Then TGA circulates ACPM advice papers and prepared advice is sent to applicant.

In the decision phase (10 business days) TGA delegate review and decision. Decision letter prepared and remaining 25% fee invoiced to applicant. If rejected applicant can appeal within 90 days of decision. In the post decision phase (40 business days) TGA final administration where Australian public assessment report (AusPAR) prepared. Applicant AusPAR C-I-C redaction. Documents published on TGA website followed by Australian register of therapeutic goods (ARTG) registration.

**Australia Regulatory Drug Approval Process
(240-260 Business Days*)**





DRUG APPROVAL PROCESS IN INDIA

New drug must meet the requirements along with NDA to FDA.

The process of approval in INDIA with emphasis on clinical trials as per drug central department, Government of India.

New Drug Application

NDA is an application submitted to the FDA for permission to market a new drug. To obtain this permission a sponsor submits preclinical and clinical test data to NDA for analyzing the drug information, description of manufacturing procedures. After NDA received by the agency, it undergoes a technical screening. This evaluation ensures that sufficient data and information have been submitted in each area to justify "filing" the application that is FDA formal review. At the conclusion of FDA review of an NDA, there are 3 possible actions that can send to sponsor: Not approvable- in this letter list of deficiencies and explain the reason. Approvable - it means that the drug can be approved but minor deficiencies that can be corrected like-labeling changes and possible request commitment to do post-approval studies. Approval- it state that the drug is approved.

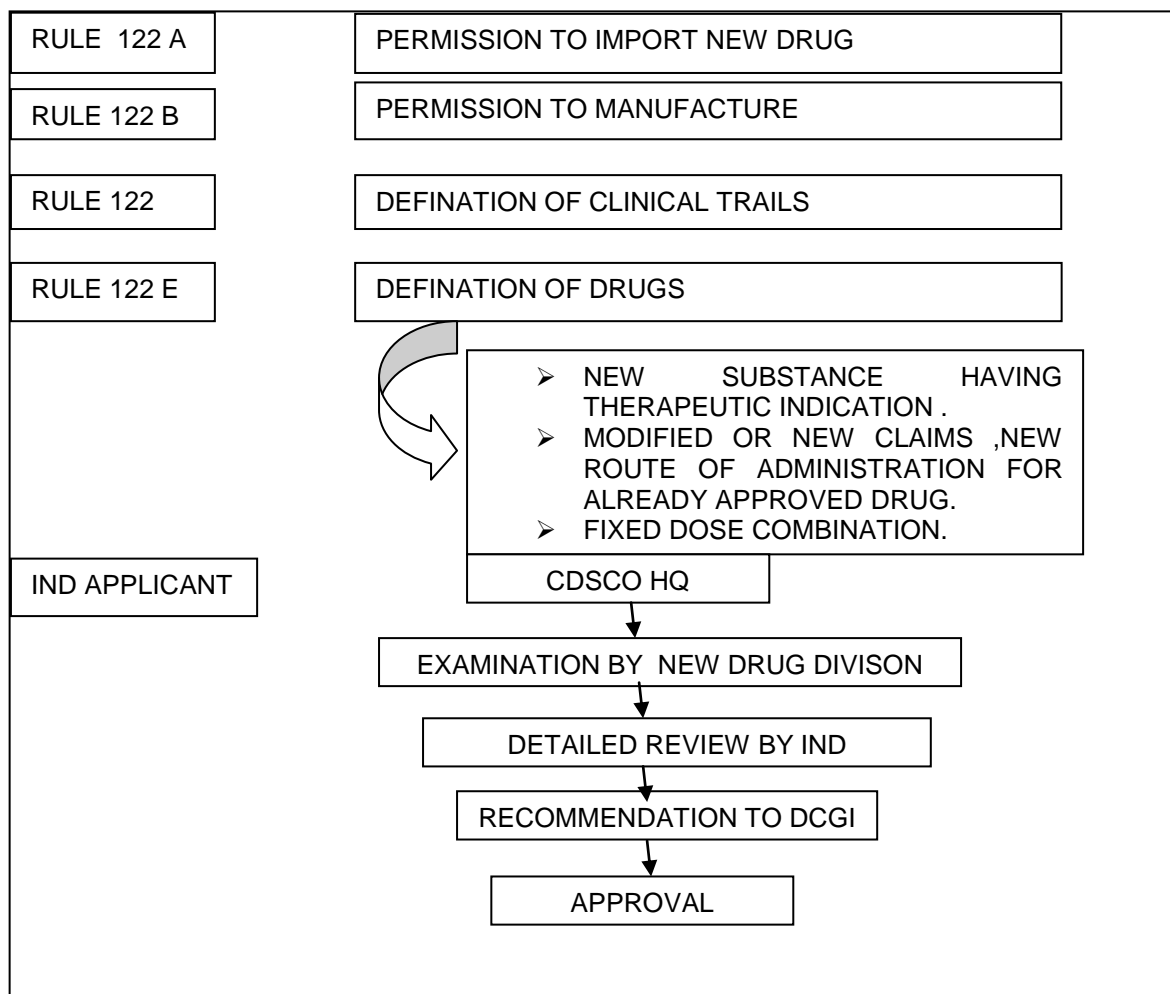


Fig: Pictorial representation drug approval process in India.

If the action taken is either an approvable or a not approvable, then FDA provides applicant with an opportunity to meet with agency and discuss the deficiencies^{8,9}

Stages of approval¹¹⁻¹⁵

1. Submission of Clinical Trial application for evaluating safety and efficacy.
2. Requirements for permission of new drugs approval.
3. Post approval changes in biological products: quality, safety and efficacy documents.
4. Preparation of the quality information for drug submission for new drug approval.

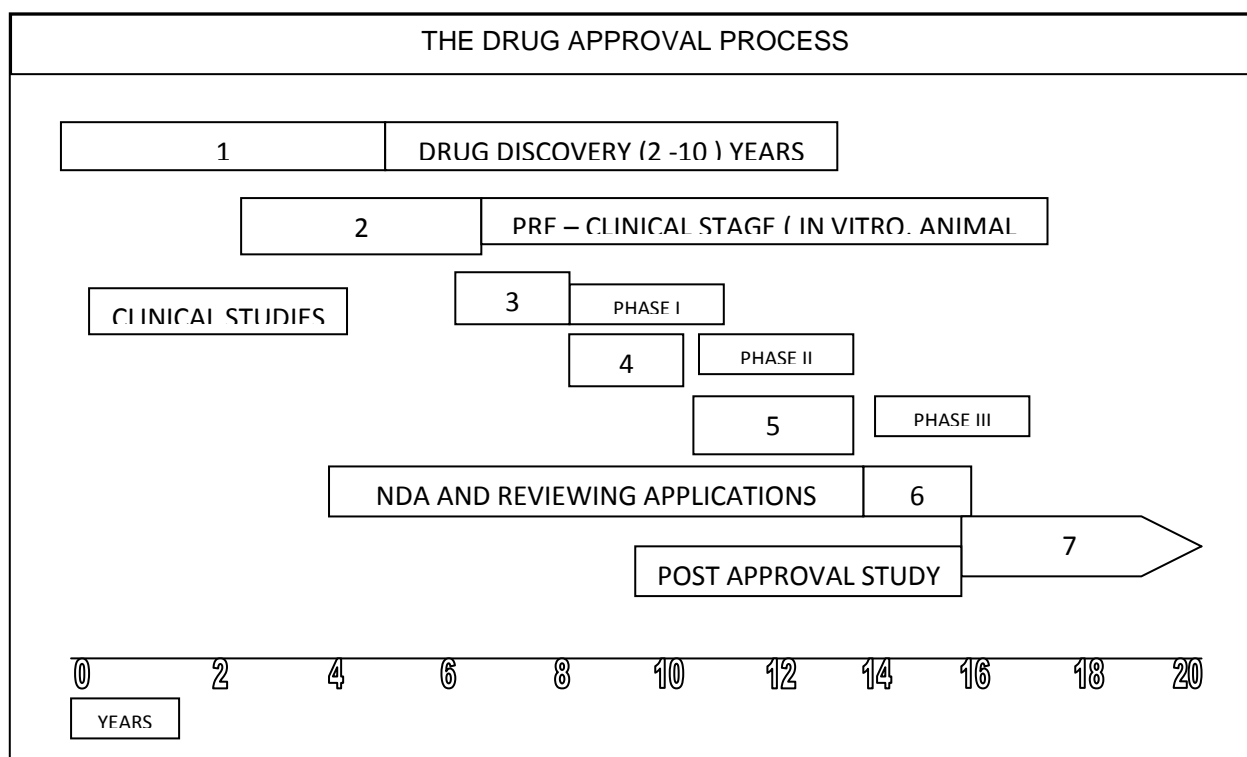


Fig : THE DRUG APPROVAL PROCESS AS A FUNCTION OF TIME

1. Submission of Clinical Trial Application for Evaluating Safety and Efficacy

All the data listed below has to be produced.

(a) Phase-I & phase- II clinical trial:

- General information
 - Introduction about company: Brief description about company
 - Administrative headquarters: Provide address of company headquarters.
 - Manufacturing Facilities: Provide address of company headquarters
 - Regulatory and intellectual property status in other countries.
 - Patent information status in India & other countries
- Chemistry manufacturing control
 - Product Description: A brief description of the drug and the therapeutic class to which it belongs.
 - Product Development
 - Strain details
 - Information on drug substance
 - Information on drug Product
- Non-clinical data: References: schedule – Y, amendment version 2005, Drugs and Cosmetics Rules, 1945
- Proposed phase-I / II studies: protocol for phase-I / II studies.

(b) Phase-III clinical trial

All the information is as same as phase-I & phase- II clinical trial

- General information
- Chemistry manufacturing control
- Non-clinical data
- Proposed phase-III studies

2. Requirements for permission of New Drugs Approval^{10,12,13}

The manufacturer / sponsor have to submit application on Form 44 for permission of New Drugs Approval under the provisions of Drugs and Cosmetic Act 1940 and Rules 1945.

The document design is as per the International submission requirements of Common Technical Document (CTD) and has five Modules.

Module I: Administrative/Legal Information

This module should contain documents specific to each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities.

Module II: Summaries

Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action and proposed clinical use. In general, the introduction should not exceed one page. The introduction should include proprietary name, nonproprietary name or common name of the drug. Substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s). It contains the CTD summaries for quality, safety, efficacy information. This module is very important, as it provides detailed summaries of the various sections of the CTD. These include: A very short introduction. Quality overall summary, Non clinical overview, Clinical over view, Non clinical written and tabulated summaries for pharmacology, pharmacokinetics, and toxicology.

Module III: Quality information (Chemical, pharmaceutical and biological)

Information on quality should be presented in the structured format described in the guidance M4Q. This document is intended to provide guidance on the format of a registration application for drug substances and their corresponding drug products. It contains of all of the quality documents for the chemistry, manufacture, and controls of the drug substance and the drug product.

Module IV: Non-clinical information

Information on safety should be presented in the structured format described in the guidance M4S. The purpose of this section is to present a critical analysis of the non-clinical data pertinent to the safety of the medicinal product in the intended population. The analysis should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information. It gives final copy of all of the final nonclinical study reports.

Module V: Clinical information

Information on efficacy should be presented in the structured format described in the guidance M4E. It gives clinical summary including biopharmaceutics, pharmacokinetics and pharmacodynamics, clinical pharmacology studies, clinical efficacy, clinical safety, synopses of the individual studies and final copy of detailed clinical study reports^{10,12,13}.

3. Preparation of the quality information for drug submission for new drug approval

- 1) Drug substance (name, manufacturer)
- 2) Characterization (name, manufacturer) Physicochemical characterization Biological characterization
- 3) Drug product (name, dosage form)
- 4) Control of drug product (name, dosage form)
- 5) Appendices
 - Facilities and equipment (name, manufacturer)
 - Safety evaluation adventitious agents (name, dosage form, manufacturer).

For the import or manufacture of new drug for clinical trials, there are several steps that have to be followed¹⁵

Application for permission to import New Drug (122-A)

1.(a). No new drug shall be imported, except under, and in accordance with, the permission granted by the Licensing Authority as defined in clause (b) of rule 21;

(b). An application for grant of permission to import a new drug shall be made in Form 44 to the Licensing Authority, accompanied by a fee of fifty thousand rupees:

Provided further that where a subsequent application by the same applicant for that drug, whether in modified dosage form or with new claims, is made, the fee to accompany such application shall be fifteen thousand rupees;

Provided further that any application received after one year of the grant of approval for the import and sale of new drug, shall be accompanied by a fee of fifteen thousand rupees and such information and data as required by Appendix 1 or Appendix 1A of Schedule Y, as the case may be.

2. The importer of a new drug when applying for permission under sub-rule (shall submit data as given in Appendix 1 to Schedule Y including the results of local clinical trials carried out in accordance with the guidelines specified in that Schedule and submit the report of such clinical trials in the format given in Appendix II to the said Schedule:

Provided that the requirement of submitting the results of local clinical trials may not be necessary if the drug is of such a nature that the licensing authority may, in public interest decide to grant such permission on the basis of data available from other countries:

Provided further that the submission of requirements relating to Animal toxicology, reproduction studies, teratogenic studies, perinatal studies, mutagenicity and Carcinogenicity may be modified or relaxed in case of new drugs approved and marketed for several years in other countries if he is satisfied that there is adequate published evidence regarding the safety of the drug, subject to the other provisions of these rules.

3. The Licensing Authority, after being satisfied that the drug if permitted to be imported as raw material (bulk drug substance) or as finished formulation shall be effective and safe for use in the country, may issue an import permission in Form 45 and/or Form 45 A, subject to the conditions stated therein;

4. Provided that the Licensing Authority shall, where the data provided or generated on the drug is inadequate, intimate the applicant in writing, and the conditions, which shall be satisfied before permission, could be considered.¹⁵

Application for approval to manufacture New Drug other than the drugs classifiable under Schedules C and C (1) (122-B)

1. (a) No new drug shall be manufactured for sale unless it is approved by the Licensing Authority as defined in clause (b) of rule 21.

(b) An application for grant of approval to manufacture the new drug and its formulations shall be made in Form 44 to the Licensing Authority as defined in clause (b) of rule 21 and shall be accompanied by a fee of fifty thousand rupees;

Provided that where the application is for permission to import a new drug (bulk drug substance) and grant of approval to manufacture its formulation/s, the fee to accompany such application shall be fifty thousand rupees only;

Provided further that where a subsequent application by the same applicant for that drug, whether in modified dosage form or with new claims, is made, the fee to accompany such subsequent application shall be fifteen thousand rupees;

Provided further also that any application received after one year of the grant of approval for the manufacture for sale of the new drug, shall be accompanied by a fee of fifteen thousand rupees and such information and data as required by Appendix I or Appendix I A of Schedule Y, as the case may be.

2. The manufacturer of a new drug under sub-rule (1) when applying for approval to the licensing authority mentioned in the said sub-rule, shall submit data as given in Appendix I to schedule Y including the results of clinical trials carried out in the country in accordance with the guidelines specified in schedule Y and submit the report of such clinical trials in the format given in Appendix II to the said schedule. The Licensing Authority as defined in clause (b) of rule 21 after being satisfied that the drug if approved to be manufactured as raw material (bulk drug substance) or as finished formulation shall be effective and safe for use in the country, shall issue approval in Form 46 and/or Form 46 A, as the case may be, subject to the conditions stated therein:

Provided that the Licensing Authority shall, where the data provided or generated on the drug is inadequate, intimate the applicant in writing, and the conditions, which shall be satisfied before permission could be considered.

3. When applying for approval to manufacture of a new drug under sub-rule (1) or its preparations to the state licensing authority, an applicant shall produce along with his application, evidence that the drug for the manufacture of which application is made has already been approved by the licensing authority mentioned in Rule 21;

Provided that the requirement of submitting the result of local clinical trials may not be necessary if the drug is of such a nature that the licensing authority may, in public interest decide to grant such permission on the basis of data available from other countries;

Provided further that the submission of requirements relating to Animal toxicology, reproduction studies, teratogenic studies, perinatal studies, mutagenicity and Carcinogenicity may be modified or relaxed in case of new drugs approved and marketed for several years in other countries if he is satisfied that there is adequate published evidence regarding the safety of the drug, subject to the other provisions of these rules.

Permission to import or manufacture fixed dose combination (122-D)

1. An application for permission to import or manufacture fixed dose combination of two or more drugs as defined in clause (c) of rule 122 E shall be made to the Licensing Authority as defined in clause (b) of rule 21 in Form 44, accompanied by a fee of fifteen thousand rupees and shall be accompanied by such information and data as is required in Appendix VI of Schedule Y.
2. The Licensing Authority after being satisfied that the fixed dose combination, if approved to be imported or manufactured as finished formulation shall be effective and safe for use in the country, shall issue permission in Form 45 or Form 46, as the case may be, subject to the conditions stated therein;
Provided that the Licensing Authority shall where the data provided or generated on the fixed dose combination is inadequate, intimate the applicant in writing, and the conditions which shall be satisfied before grant of approval/permission could be considered.

Application for permission to conduct clinical trials for new drug (122-D)

1. No clinical trial for a new drug, whether for clinical investigation or any clinical experiment by any Institution, shall be conducted except under, and in accordance with, the permission, in writing, of the Licensing Authority defined in clause (b) of rule 21.
2. An application for grant of permission to conduct,-
 - Human clinical trials (Phase-I) on a new drug shall be made to the Licensing Authority in Form 44 accompanied by a fee of fifty thousand rupees and such information and data as required under Schedule Y;
 - Exploratory clinical trials (Phase-II) on a new drug shall be made on the basis of data emerging from Phase-I trial, accompanied by a fee of twenty-five thousand rupees;
 - Confirmatory clinical trials (Phase-III) on a new drug shall be made on the basis of the data emerging from Phase-II and where necessary, data emerging from Phase-I also, and shall be accompanied by a fee of twenty-five thousand rupees:
Provided that no separate fee shall be required to be paid along with application for import/manufacture of a new drug based on successful completion of phases of clinical trials by the applicant.
Provided further that no fee shall be required to be paid along with the application by Central Government or State Government institutes involved in clinical research for conducting trials for academic or research purposes.
3. The Licensing Authority after being satisfied with the clinical trials, shall grant permission in Form 45 or Form 45A or Form 46 or Form 46-A, as the case may be, subject to the conditions stated therein:
Provided that the Licensing Authority shall, where the data provided on the clinical trials is inadequate, intimate the applicant in writing, within six months, from the date of such intimation or such extended period, not exceeding a further period of six months, as the Licensing Authority may, for reasons to be recorded, in writing, permit, intimating the conditions which shall be satisfied before permission could be considered:

Suspension or cancellation of Permission / Approval (122-DB)

If the importer or manufacturer under this Part fails to comply with any of the conditions of the permission or approval, the Licensing Authority may, after giving an opportunity to show because why such an order should not be passed, by an order in writing stating the reasons there for, suspend or cancel it.

Appeal (122-DC)

Any person aggrieved by an order passed by the Licensing Authority under this Part, may within sixty days from the date of such order, appeal to the Central Government, and the Central Government may after such enquiry into the matter as is considered necessary, may pass such order in relation thereto as it thinks fit.¹⁻⁴

APPROVAL PROCESS OF NEW DRUG IN CHINA²³

China-Economic reformation in China has being 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.

There are five types of drug registration application in China:

1. New drug application
2. Generic drug application
3. Imported drug application
4. Supplemental application
5. 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.

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.

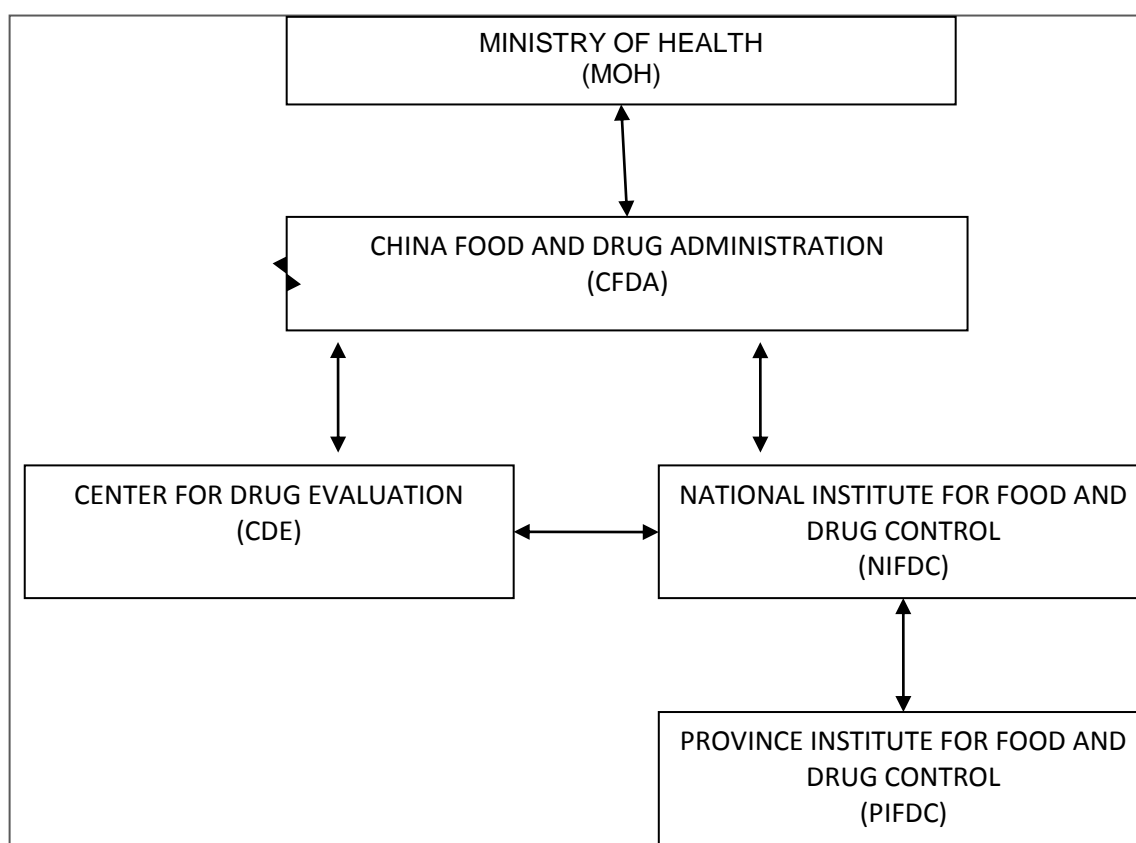
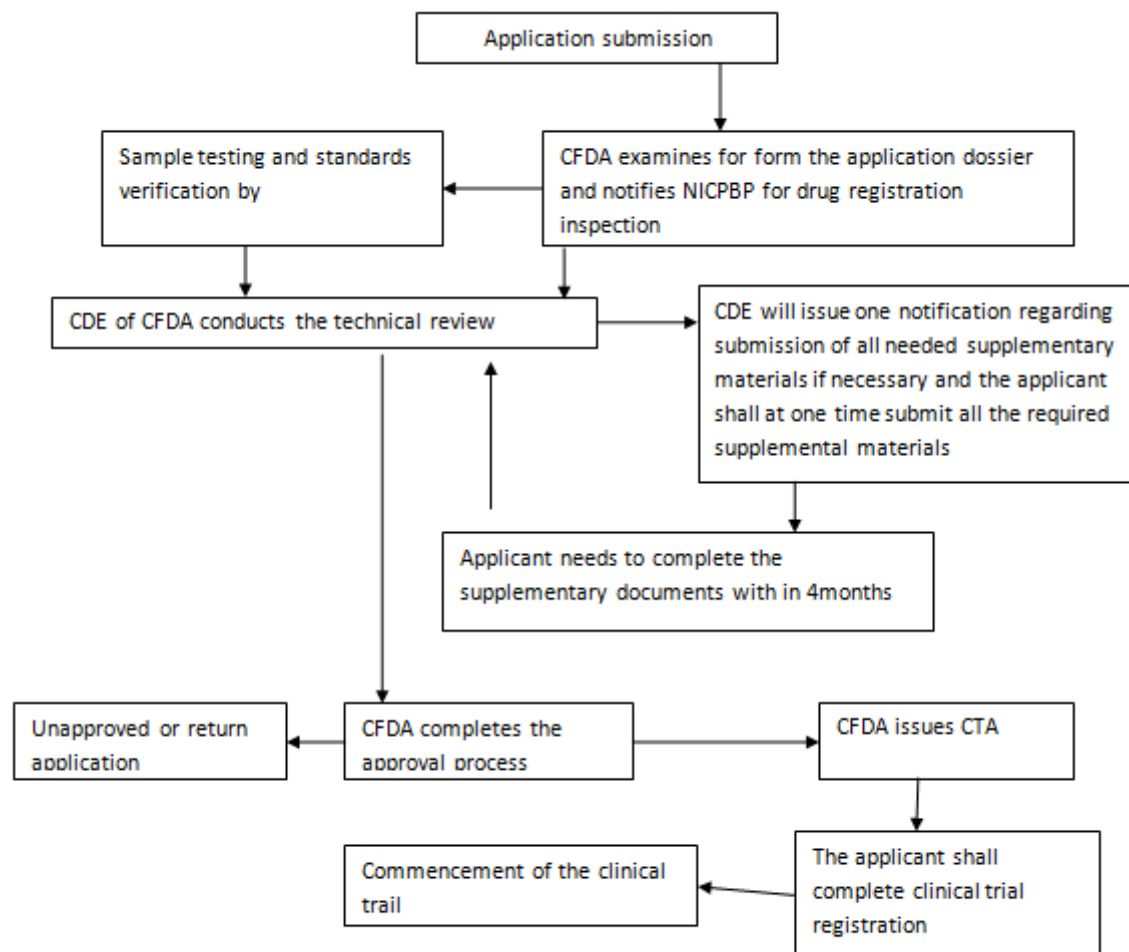
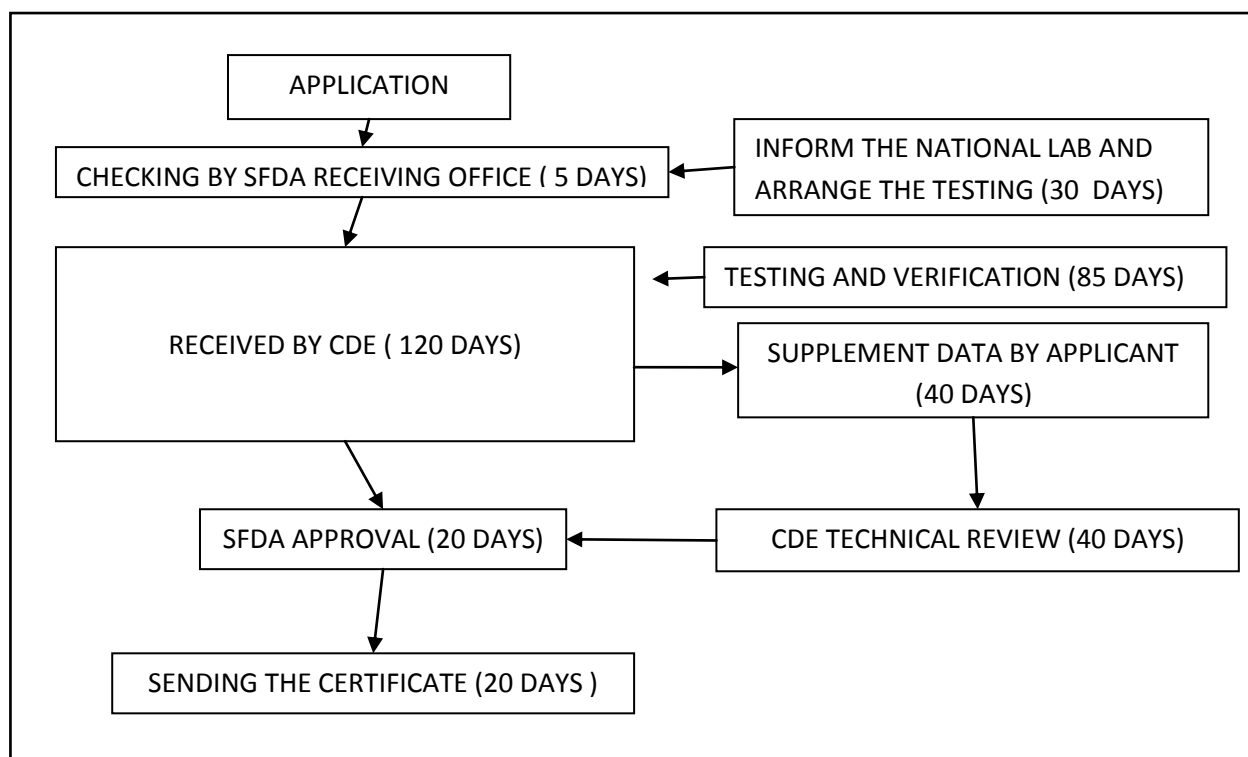


Fig: Key Regulatory Players in China¹⁶⁻²²

REGISTRATION PROCEDURE FOR CTA

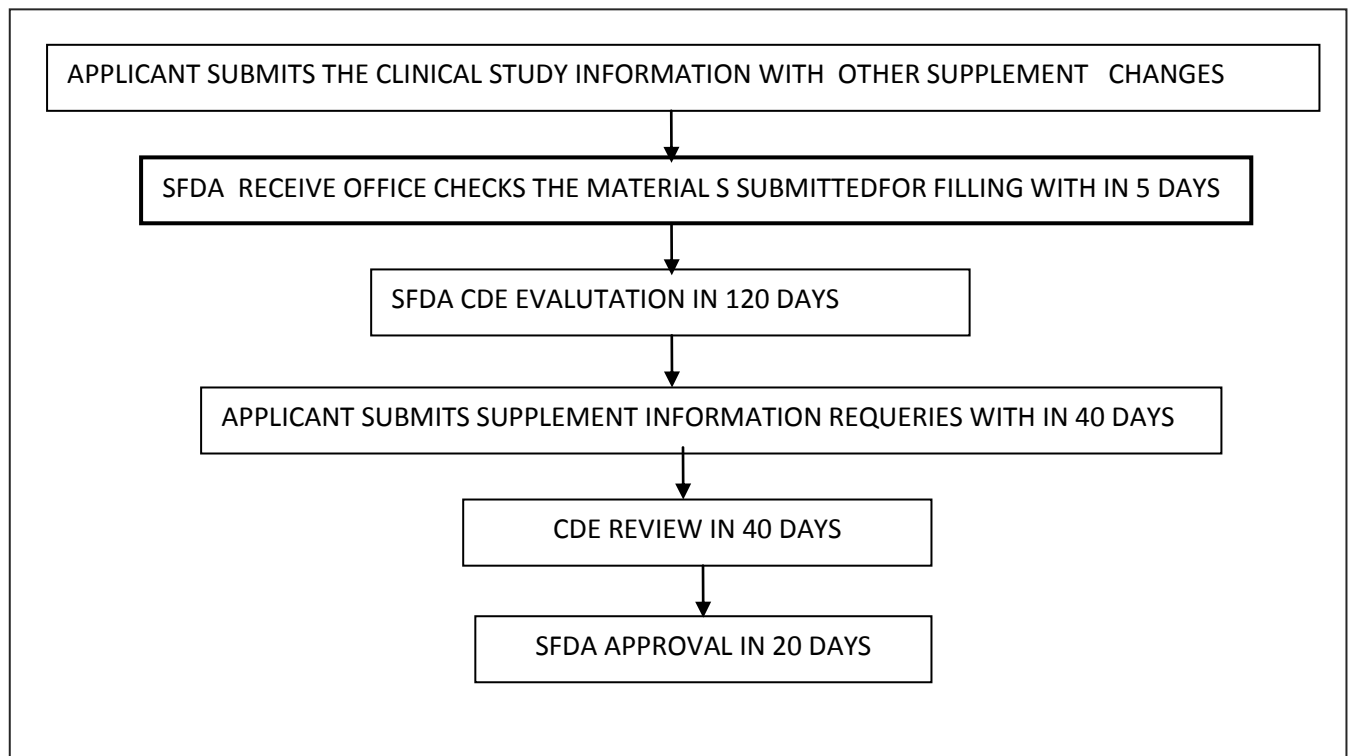
**Clinical Study**

The Centre for Drug Evaluation will carry out a technical review of the test report and overall documentation which usually takes from 40 to 160 days to complete, depending on the product. The review report will be sent to the CFDA with recommendation on whether the product is subject to a clinical trial or bioequivalence study in China. Further information can be found in the Measures of the Administration of Drug Registration which outlines the requirements for clinical studies. If the Centre for Drug Evaluation deems that no clinical study is needed, the application will enter the final registration phase. In summary, the clinical study can be divided into 4 phases; however it is beyond this document to give a comprehensive introduction to clinical trials in China. Generally, phase I of the study needs between 20 to 30 subjects, phase II is approximately 200 subjects, phase III is 300 subjects, and phase IV is conducted as a post-marketing study investigating around 2000 subjects. For class III pharmaceutical products, a study with 100 pairs of subjects is required. For a bioequivalence study, generally 18-24 subjects are needed. Once the applicant receives approval for the clinical study, the applicant is free to choose the hospitals where the clinical study will be conducted from a list of designated clinical research hospitals or medical institutions listed on the CFDA website. It is a requirement that the clinical study needs to be conducted at a minimum of two different hospitals. The clinical study should be conducted



Flow chart: Imported drug registration process (Before clinical study)

in compliance with Good Clinical Practice (GCP). All the pharmaceutical products used for the clinical study need to be tested, either by self-testing by the manufacturer or contracted to a designated testing laboratory coordinated by the NIFDC. After completing the clinical study, the clinical study plan, trial protocol, the approval documents by the Ethical Committee, together with patient consent forms and study report will form part of the drug registration application. It is difficult to give general statements about the timeframe for a Chinese clinical trial, as this will depend on availability of subjects, nature of disease, schedule of the hospital, etc. After completing the clinical study and pharmaceutical registration test, the applicant will need to fill in the drug registration form again and submit all documentation to the SFDA. The SFDA's Drug Evaluation Centre will review and evaluate all the submitted information. In some cases, the Drug Evaluation Centre will involve external experts in the evaluation of the pharmaceutical product. Once the Drug Evaluation Centre has passed its final judgment, the file is transferred to the SFDA for final approval. It is ultimately the decision of the SFDA to make its administrative decision for granting certification of the product or not. If the application is not approved, the applicant can apply for re-evaluation within 60 days. The pharmaceutical registration certificate is valid for 5 years and re-registration should be applied for at least 6 months prior to the certificate expiring. Re-registration should be submitted with all information of post approval assessments in terms of the safety, efficiency and quality of the product done or collected within the 5 year validity period. In addition to the testing fee for the pharmaceutical registration test, and expenses for clinical trials, the drug registration fee amounts will be paid directly to the SFDA.



Flow chart: Imported drug registration process (after clinical study)

Imported drug registration process (after clinical study)

The first step in this process is to submit an application to the CFDA for a Clinical Trial Application (CTA). The CFDA will conduct a preliminary review of the submission package and then transfer the dossier to the Center for Drug Evaluation (CDE). Reviewers with background in pharmaceuticals, pharmacology and clinical study will run a technical review, while local sample testing will also be conducted in parallel. Few CTAs would pass through the CDE review in one single round. However, most applications will receive supplement notice(s) in writing to request additional information for further assessment. In such case, CDE will allow a 4-month period for applicant to gather and submit additional requested information to CDE. This entire CTA step usually takes at least 125 working days.

The second step in drug registration is Production Application (or Imported Drug License Application), which involves submitting a clinical report and other relevant dossiers to obtain an imported drug license. The process itself is basically the same as the CTA step. This second step will take approximately 145 days.¹¹

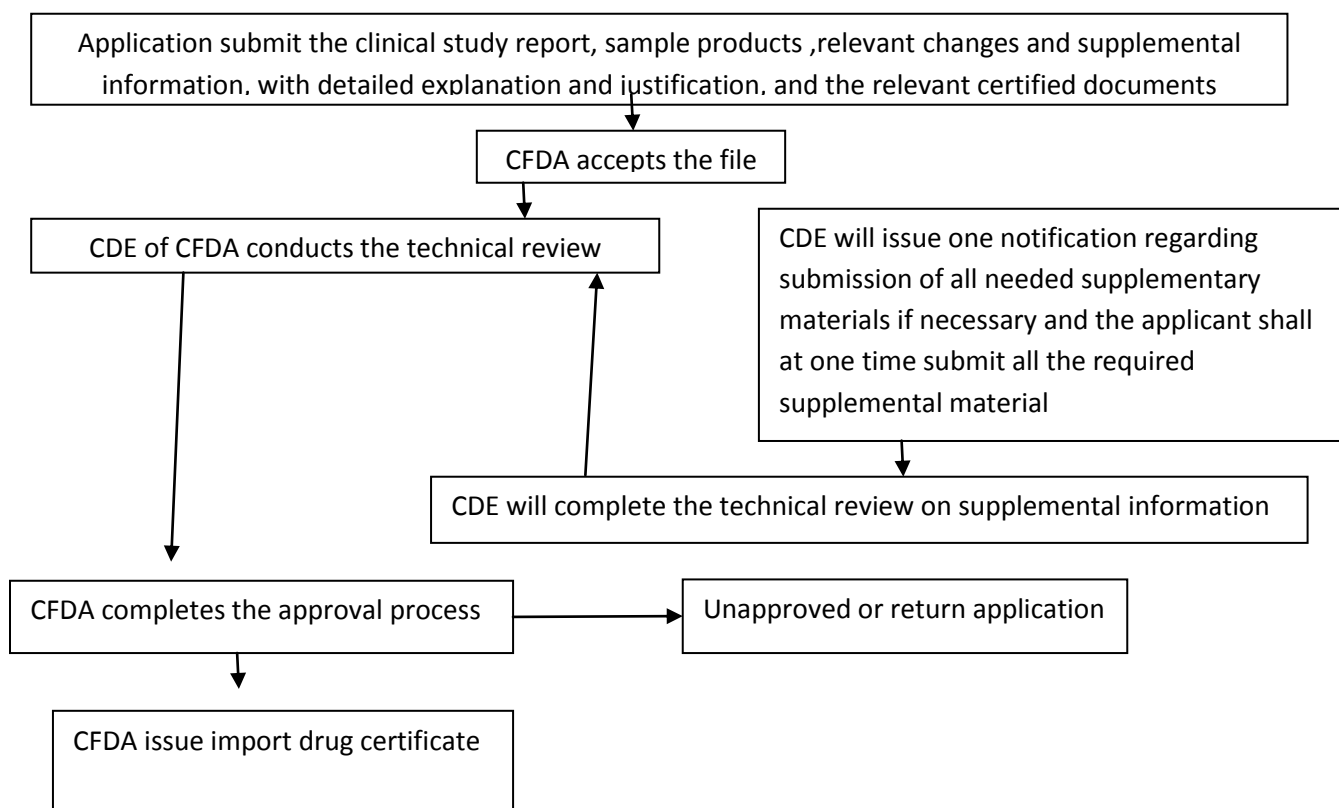


Fig: Registration Procedure for NDA

APPROVAL PROCESS OF GENERIC DRUG IN CHINA²⁴⁻²⁸

Application Procedure Generic drug applications must be filed by the drug manufacturer in the provincial FDA (PFDA) where the applicant is located. The PFDA serves as the receiving office for the generic application and determines whether the application dossier is in proper order. If the requirements are met, the PFDA provides notification of acceptance of the drug registration application. If the requirements are not met, the applicant is provided with an explanation of the reasons for rejection, and the opportunity to reapply. Within five days of acceptance of the application, the PFDA will conduct an on-site

Inspection of the production site, as well as the original drug research data, and take samples of three consecutive batches to send to the Drug Control Institute for inspection. The sample products are required to be manufactured in a facility with Good Manufacturing Practice (GMP) certification. After completing examination of the application dossier, the PFDA will submit the dossier along with its examination recommendation, verification report and results of its inspection of the production site to the SFDA Center for Drug Evaluation (CDE) within 30 days. CDE will organize pharmaceutical, medical and other technical staff to examine the verification recommendation and the application dossier, and may request that the applicant provide supplemental information if necessary. At the same time, the Drug Control Institute tests the sample products and provides its sample test report to CDE, the PFDA and the applicant. CDE prepares a general examination recommendation based on the technical examination recommendation, production site inspection information and sample test report, and then submits to SFDA along with related data. SFDA then makes its approval decision based on the general recommendation and issues a Drug Approval Number (if no clinical trials are needed), or a Clinical Trial Approval (if clinical trials are needed). Upon completion of clinical trials, the applicant must then submit the clinical trials data to SFDA for issuance of a Drug Approval Number. For drugs that do not meet safety requirements, the Amended Regulation grants SFDA authority to suspend acceptance or approval of the generic drug application.

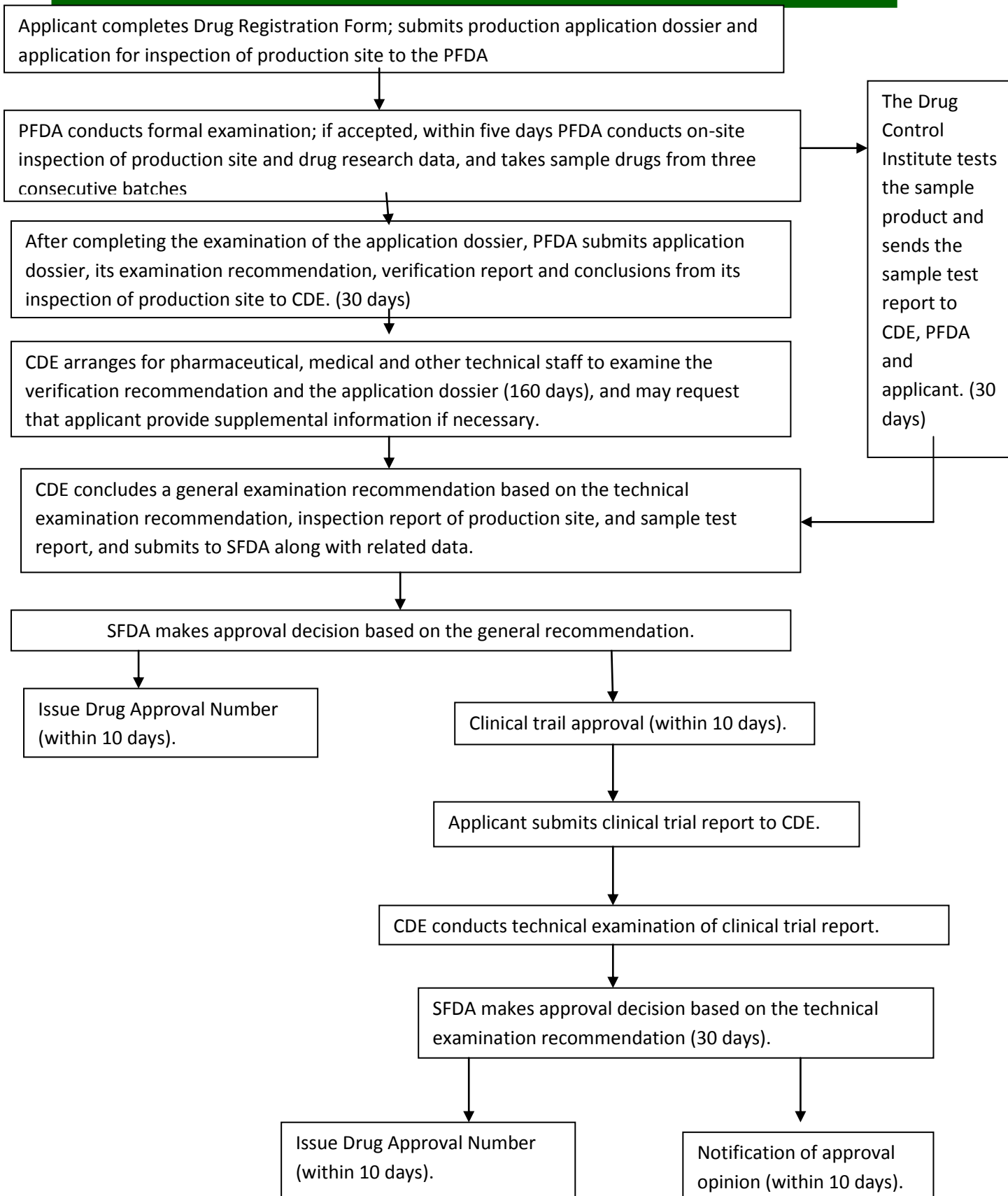


Fig: Generic Application Approval Flow Chart & Timeline

DRUG APPROVAL PROCESS IN SAUDI ARABIA²⁹**Registration Rules**

Drug sector at SFDA sets the rules for registering different types of drugs. Such rules are developed by examining the current and future competencies of its evaluators. These rules will help the applicants to decide whether to submit their drug applications or not.

The following rules/conditions if met, the submitted drug application will be accepted:

1. New Drug and Biological (either registered in an SRA or not)
2. Generic Drug that is equivalent to the registered innovator in an SRA (the drug shall be registered as "New Drug" because the API is not registered in KSA)
3. Biosimilar drug only if it is manufactured locally
4. Biosimilar drug if registered in an SRA
5. Combination products (2 or more API):
 - a) If the API's are registered in KSA as single drugs (with the same strength, dosage form and therapeutic indication), the application is considered Generic.
 - b) If one or more of the API's are not registered in KSA, the application is considered New Drug.

Notes:

- Performance targets will differ depending on the type of drug
- Generic drugs that are not equivalent to the innovated product in the strength, are considered Generic (as long as the API is registered in KSA)
- Generic drugs that are not equivalent to the innovated product in the dosage form, are considered New Drug – Known active substance (as long as the API is registered in KSA).

Submission Process

The process of submitting a NEW drug application to the SFDA consists of three major steps:

1. Online submission of the APPLICATION FORM,
2. The PRODUCT FILE delivered in person,
3. DRUG SAMPLES.

Important Note

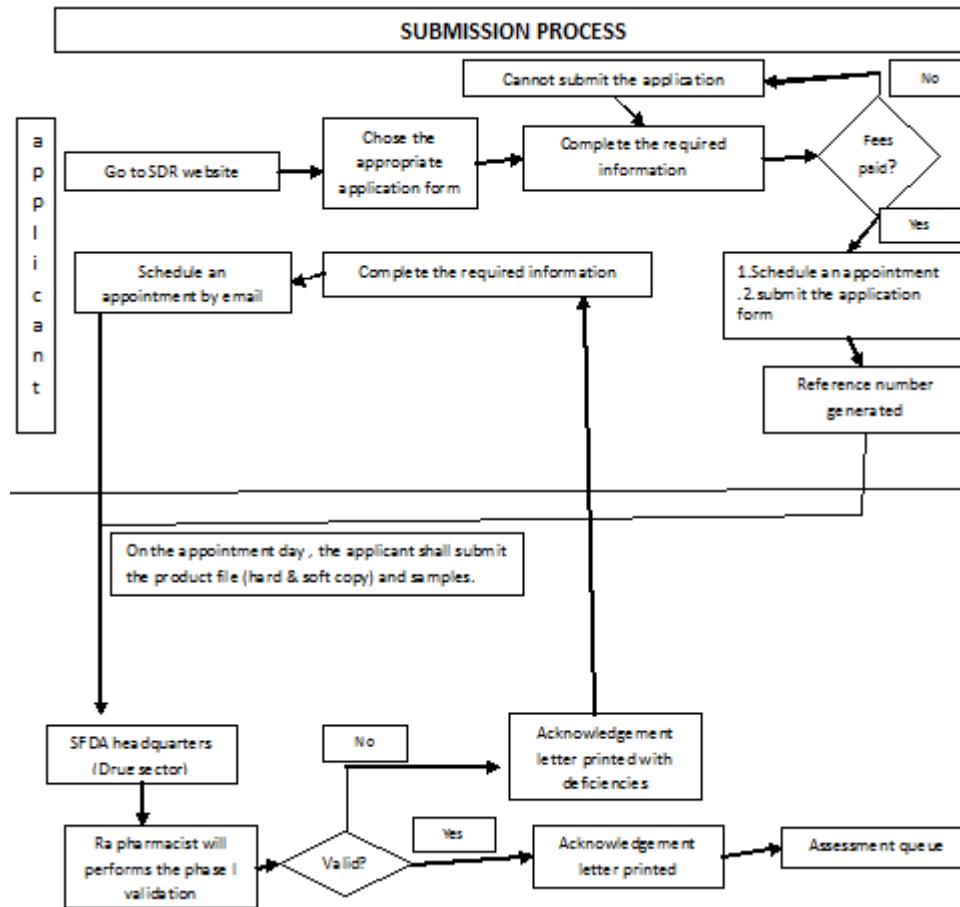
All days mentioned throughout this document are WORKING days (subject to change).

Step by step procedure

1. Applicant shall go to the Saudi Drug Registration system (SDR) website (<http://sdr.sfda.gov.sa/>).
2. Login to apply (each applicant should have a user ID and a password)
3. Choose and complete the appropriate application form:
 - The application form can be saved partially as the applicant may complete it in several steps.
4. Then, the applicant has to pay the submission fee (through SADAD Payment System) in order to submit the application form and schedule an appointment to deliver the hard and soft copy of the product file:
 - Submission fees are mandatory in order to proceed to the next step.
 - The applicant can reschedule 3 weeks before the appointment. An automatic reminder will be sent 3 days before the appointment.
 - A reference number will be generated, and this number should always be used with regard to any communication with the SFDA.
5. At the appointment, the applicant will deliver the product file along with the samples.
6. The Regulatory Affairs Pharmacist will validate (Phase I) the following:
 - a. The application form
 - b. The product file (hard and soft copy)
 - c. The samples
 - If the above are valid, an acknowledgment letter will be generated and given to the applicant. The drug application will enter the queue.
 - If some of the above are missing or not satisfactory, an acknowledgment letter will be generated and given to the applicant stating the deficiencies. The applicant will have a period of 90 days to complete the requirements and the drug application will not be queued. When the required information is met, an appointment (completion appointment) is requested by email (sdr.drug@sfda.gov.sa), and the step no 6 will be repeated again.

Notes

- Currently for renewal applications, no appointment scheduling is required. And for the variation applications, neither payment nor appointments are required.
- Refer to the Guidance for Submission for more details on preparing the drug file.



Flow chart of submission process

Marketing Authorization Application (MAA)

The Market Authorization Application for the different drug submission types will be subjected to the following processes:

A. Validation (Phase II)

1. The product file will be validated to ensure that all information provided are according to the requirements and/or guidelines:
 - The completed file will proceed to the next steps in parallel – assessment, testing and inspection.
 - If any information is missing or incorrect, the applicant will be notified electronically. The applicant will be given an opportunity to complete the file within 90 days. Otherwise, the file will be rejected.
2. Performance target: 10 days for all drug submission types.

B. Assessment

1. The product file will be distributed by the product manager to THREE groups: Quality, Safety and Efficacy.
2. Quality assessment will be performed by a quality group. Once completed, a report will be forwarded to the product manager.
3. Safety assessment will be performed by a safety group. Once completed, a report will be forwarded to the product manager.
4. Efficacy assessment will be performed by an efficacy group. Once completed, a report will be forwarded to the product manager.

5. If a clarification is required, an electronic "Inquiry Form" will be forwarded to the applicant through the product manager. The response should be received within 90 days. Otherwise, the application will be rejected.
6. The reports (i.e. recommendation for approval or rejection) will be forwarded to the secretary of the Registration Committee.
7. Performance target:
 - a) Generics: 120 days
 - b) New Drugs: i. Registered in a Stringent Regulatory Authority (SRA): 245 days ii. Not registered in SRA: 370 days
 - c) Biologicals:
 - i. Registered in SRA: 245 days
 - ii. Not registered in SRA: 370 days
 - d) Radiopharmaceuticals: 245 days
 - e) Veterinary drugs: 150 days
 - f) Herbal & Health products: 110.

C. Testing

1. Samples received by SFDA headquarters will be sent to the laboratory.
2. If more information, clarification or additional samples are needed, an electronic "Inquiry Form" will be forwarded to the applicant through the product manager. A response should be received within 90 days.
3. The results will be written in a report and forwarded to the product manager.
4. Performance target: 90 days for all drug submission types.

Note:

- Testing will not delay the registration of a product
- The 1st batch imported after approval will be tested and the company will be notified of the results within 35 days. However, the company should not distribute the product during this period. After 35 days, the company may distribute the product under their own liability.

D. Inspection

1. The product file will be forwarded to the Head of the inspection unit:
 - a. If more information or clarification is required, an electronic "Inquiry Form" is forwarded to the applicant through the Inspection unit. A response should be received within 90 days.
2. Inspection department will check the manufacturing line:
 - a) If the manufacturing line has been approved (valid certificate from KSA MoH, SFDA or GCC-DR), the line would not be inspected and the head of the inspection unit will inform the product manager
 - b) If the manufacturing line is not approved:
 - i. The head of the inspection unit will schedule a visit for inspection (depending on the time available for both inspectors and the company).
 - ii. After the visit, the inspection report will be written and forwarded to the Head of inspection unit.
 - iii. Head of inspection unit will send the inspection report to the company (please, refer to the Inspection guidance).
3. The final inspection report will be forwarded to the product manager.
4. Performance target:
 - a) Generics: 120 days
 - b) New Drugs: 245 days
 - c) Biologicals: 245 days
 - d) Radiopharmaceuticals: 245 days
 - e) Veterinary drugs: 150 days
 - f) Herbal & Health products: 110 days

After the Assessment and Inspection reports are completed, the product file will be forwarded to the pricing department.

E. Pricing

1. The Pricing department handles pricing requests and ensures that all pricing requirements are met (such as the presence of a valid, updated and authenticated Price Certificate (Form-30) and a product sample in its final pack form). However, if more information or clarification

is required, an electronic "Inquiry Form" will be forwarded to the applicant through the product manager. A response should be received within 90 days.

2. The Pricing department will calculate the price of each concentration and/or pack size of different product from a pricing & economic perspectives according to the SFDA's pricing rules.
3. The Pricing minute is then prepared to be discussed with the Pricing Committee.
4. If the committee ask for more information or clarification, an electronic "Inquiry Form" will be forwarded to the applicant by the pricing department through the product manager. A response should be received within 90 days.
5. The approved price by the committee will be written in a report and forwarded to the product manager.
6. Performance target: 20 days for all drug submission types

F. Product Licensing

1. Product manager will receive all reports from departments and forward them to the secretary of the "Registration Committee":
 - a. The secretary of the Registration Committee will add the product to the agenda of the next available meeting.
 - b. At the meeting, the Registration Committee will either recommend approval, rejection or ask for further information – if needed.
 - c. Performance target: 12 days for all drug submission types
2. The meeting minutes
 - d. Will be sent to the SFDA CEO for approval.
 - e. Then, the Product Licensing department will issue a marketing authorization.
 - f. Performance target: 3 days for all drug submission types

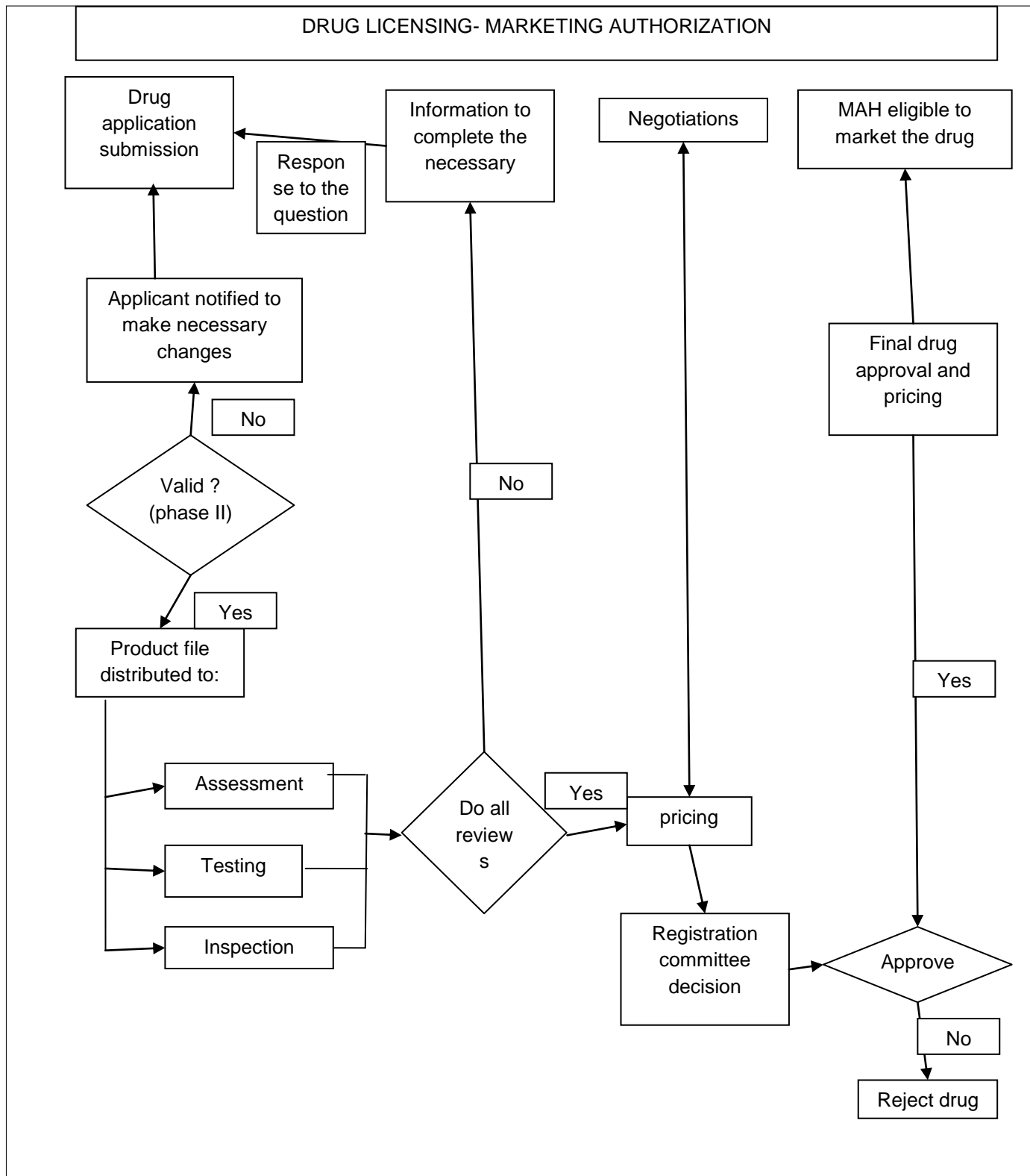
Total performance target

- a) Generics: 165 days
- b) New Drugs:
 - i. Registered in a Stringent Regulatory Authority (SRA): 290 days
 - ii. Not registered in SRA: 415 days
- c) Biologicals
 - i. Registered in SRA: 290 days
 - ii. Not registered in SRA: 415 days
- d) Radiopharmaceuticals: 290 days
- e) Veterinary drugs: 175 days
- f) Herbal & Health products: 155 days

Note: the performance target in any step will STOP if a clarification or information is needed from the applicant, and resume after receiving the response.

Appeal Process

The applicant has the right to appeal against the decision within 60 calendar days by submitting a letter including the scientific justifications supporting the appeal, in addition to fee payment (through SADAD Payment System). However, The Pricing Committee may negotiate the approved price with the company – if needed and upon the request of the applicant.



Schematic figure showing the different levels of getting a marketing authorization

CONCLUSION

From the above review it can be concluded that, all clinical studies reports and related information regarding the approval of new drug in different countries should provide the necessary requirements. Generally, the drug approval process comprised mainly the two steps, application to conduct clinical trial and application to the regulatory authority for marketing authorization of drug.

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