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Review Article

Good Practices in Management of deficiencies in CTD dossier and comparative study for US, EU and Australia

Pooja Vinod Chaudhari [a], Jitendra Kumar Badjatya[b,*]

[a] *Nandan Villa, Flat no 3, Near Patidar Bhavan, Vaidya Nagar, Dwarka, Nasik, India.*
[b] *Umedica Laboratories Pvt. Ltd., Phase-2 GIDC Vapi, Gujarat, India-396191*

Abstract

This topic aims at reviewing the drug and drug product filing and obtaining USFDA EMEA and TGA approval and its effective role to improve the standards which are laid by them. The respective Regulatory Agency approves the new/generic drug products that govern respective market before introduction of particular product into the market. The Regulatory Agency approves the entire new drug product to be safe and effective before marketing. USFDA is the Regulatory Agency which is responsible for the regulation of food and drug product in USA. EMEA is the Regulatory Agency which is responsible for the regulation of food and drug product in Europe. TGA is the Regulatory Agency which is responsible for the regulation of therapeutic goods in Australia.

A dossier contains detail information about the drug substance and drug product and result of studies that are carried out in development process. For getting market authorization has to be submitted to the respective regulation bodies. Due to various regulations, ICH introduced CTD for such countries that come under it. CTD is critical for dossier submission. For regulatory submission that is to be accepted in all ICH countries.

CTD provides standardized structure. CTD makes filing easier globally. But there are differences in dossier submission requirements in these countries i.e. Module I is country specific and other regional guideline are also considered while compiling dossier application.

Keywords: Dossier Registration, CTD, Chemistry Manufacturing Control (CMC), USFDA, EMEA, TGA.

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*Corresponding author Tel.: +91-7096160846;
E-mail address: jeetbadjatya@gmail.com (J. K. Badjatya).

1. Introduction

CTD is a set of specification for a dossier for registration of medicines. CTD was developed by International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH). CTD was developed by European Medicine Agency (EMA, Europe), Food and Drug Administration (FDA, US) and Ministry of Heath, Labour and Welfare (Japan). It was adopted by TGA in 2004. (1)

The agreement to assemble all the Quality, Safety, and Efficacy information in a common format (called CTD) has revolutionized the regulatory review process led to harmonized electronic submission that in turn enabled implementation of good review practices. For industries, it has eliminated the need to reformate the information for submission to the different ICH Regulatory Authorities.

In July 2003, CTD became mandatory format for New Drug Application in Europe and Japan and strongly recommend format of choice for NDAs submitted to FDA, US. (2)

CTD is organized into 5 modules-

Module 1- Administrative section (not a part of CTD as it is regional specific)

Module 2- Quality overall summaries

Module 3- Quality

Module 4- Non Clinical Study Reports

Module 5- Clinical Study Reports

Module 1 is region specific and Module 2, 3, 4, 5 are intended to be common for all regions.

CTD TRIANGLE

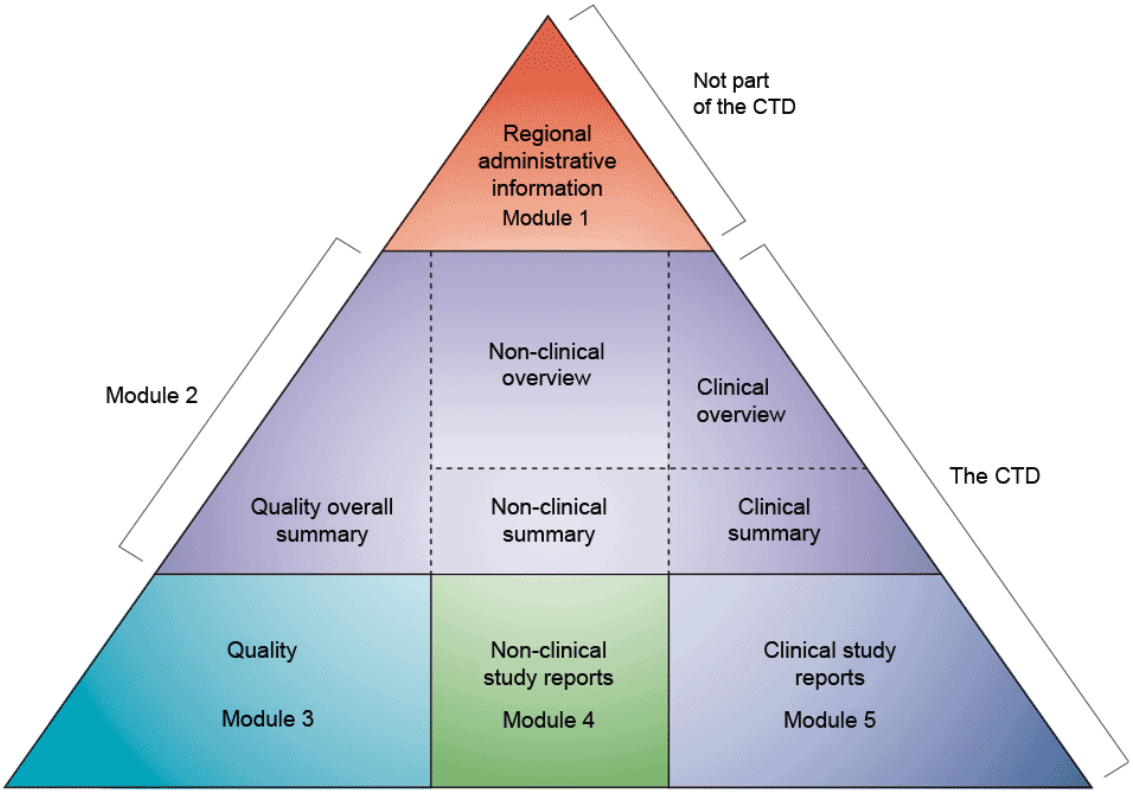


Figure 1. The CTD Triangle

The brief contents of CTD and major requirements for various regions are tabulated.

Table 1 Difference of CTD structure in US and Australia

US CTD	Australia CTD	DESCRIPTION	REMARKS
Module 1- Administrative Information	Module 1- Administrative Information and Prescribing Information	Contains documents that are specific to each region. This module is not a part of CTD. Basically consists of administrative documents like Application form, legal documents(GMP, Licenses etc.) labeling etc.	Required for generics and New Drug
Module 2- CTD Summaries	Module 2- CTD Summaries	This module summarizes the Module 3, 4 and 5. It includes Quality Overall summary, Non Clinical Overview and summary and Clinical Overview and summary. The summary provides reviewer the abstract of documents provided in the whole application.	Required for generics and New Drug. For generics summary on Quality part only required.
Module 3- Quality	Module 3- Quality	The documents related to Chemistry, Manufacturing and Control of both Drug Substance and Drug Product are included in this module.	Required for generics and New Drug
Module 4- Non clinical study reports	Module 4- Non clinical study reports	Non Clinical Study Reports- Data on pharmacologic, pharmacokinetic, and	Not required for generics.

		toxicological evaluation of the pharmaceutical product is provided.	
Module 5- **Clinical study reports**	Module 5- Clinical study reports	Clinical Study Reports- A clinical assessment of the clinical data and related reports is provided in this module.	Not required for generics except BE study.

In CTD format, harmonizing the quality information mainly includes Chemistry Manufacturing and Control (CMC) that is to be submitted in an application format. C: Chemistry means Composition of drug product. M: Manufacturing means how to manufacture the product/formulation. C: Control means ensures whether the drug products meet the predetermined specification/quality attributes.

Importance of CMC Section in CTD Dossier

- For any marketing application or clinical trials CMC (chemistry, manufacturing and controls) section is a very important and detailed section.
- If the manufacturing process cannot be shown to its highest quality standard and do not satisfied the regulators need as well as product have not their quality standard as mentioned in Pharmacopoeia than it might be chance to drug may lost the marketing approval.
- So it is important to show the standard quality process and parameter of drug manufacturing details and other parameter cover in module 3 Quality contain Chemistry, manufacturing and Control.
- The chemistry, manufacturing and controls (CMC) section is a very important part of any clinical trial or marketing application. Drugs can be denied marketing approval if the quality of the product and the manufacturing process cannot be shown to be of a sufficiently high standard to satisfy regulators.
- The ICH guideline Q1A(R2) (Stability Testing of New Drug Substances and Products) defines the stability data package required for new drug substances and products submitted for approval in each of the major regions that accept the ICH guidelines (i.e., US, Japan and EU). (3)

2. Common Dossier deficiency in CTD (3,4)

Queries in USA and EMEA

- The Qualitative & Quantitative certificate of a colorant needs to be appropriately provided.
- Polymorphism, Stereochemistry, Isomerism studies and discussion on the drug substance used in formulation is absent.
- Although preservatives are used, microbial limit tests and such other information are not provided in the pharmaceutical development data or later in the commercial scale batch manufacturing specifications.
- PDR (Pharmaceutical development reports) are not complete.
- The development report should be prepared by taking QbD into consideration.
- Pathogen Count and Total Count not provided.
- Genotoxic impurities needs to be studied which may arise from the Drug product.
- Existence/absence of polymorphism and chirality is not discussed.
- TSE/BSE declaration is not provided for the sensitive Excipients (e.g. Mg-stearate)
- The spectral data such as IR, NMR, Elemental Analysis, XRD as a means for evidence of chemical structure is not provided.
- API: Spectral graphs for IR, NMR, UV Spectra studies performed are not clear and interpretation of the same is incomplete.
- Acetone, Methanol and IPA have been used in the synthesis. However, these solvents are not analyzed for chance contamination of Class I solvents from which they are prepared.
- For the synthesis of the API products, Class I solvent Benzene is used. But the residual limits for the same are not checked at any point.
- The catalysts such as Palladium/Platinum are used in the synthesis of the products. The residual limits for the same are not described.

Queries and Responses in Australia

a) Control of excipient:

Query-The finished product manufacturer's acceptance specification for hypromellose includes acceptance limits for all substitution types (1828, 2208, 2906 and 2910) but the COA indicates that the criteria for substitution type 2910 (methoxy group: 28.0 – 30.0%; hydroxypropoxy group: 7.0 – 12.0%) are applied.

Response- Please amend the specification for hypromellose to include the acceptance criteria for the type of hypromellose used in the proposed formulation **(substitution type 2910)**, unless otherwise justified.

b) Finished Product Specification:

Query- BP identification test by IR used for identification of the active ingredient in the drug product at release is acceptable.

Response- This identification test should also be included in the expiry specifications for the purpose of testing by the TGA.

c) Assay:

Query-The proposed limits for content of Product X at release and 'stability' (95.0 – 105.0 % LC) comply with the BP monograph requirements, as specified by TGO78. However, the application of common release and expiry limits does not take into account any decreases that may be observed during long term storage of the tablets. In this respect, a tighter lower limit should be applied at batch release to ensure that a tablet batch released with an active ingredient content at the lower limit complies with the limit of 95.0% LC following full term storage at the maximum recommended storage temperature (30°C). Unless otherwise justified, the proposed limits for content of Product at release should be revised to include a suitable differential between the lower release and expiry limits to accommodate analytical variability as well as the potential maximum decrease to be observed upon 36 months storage at 30°C. Regression analysis of these results should be used as the basis of the calculation of this differential, with the limit set based on the worst case scenario.

Response-Different limits as should be provided and limit should be stringent during release specification.

d) Impurities:

Query-The proposed specifications for related substances (impurities A, B & G: NMT 0.3% each; any other impurity: NMT 0.2%; and total impurities: NMT 1.0%) comply with the BP monograph requirements and are therefore acceptable for expiry purposes. However, as with the Assay, the application of common release and expiry limits does not take into account either the potential for increase during long term storage for the duration of the tablets' shelf life or analytical variability. In the stability studies provided, the impurities A, B and G were not detected at any time point but levels of 'any other impurity' and 'total impurities' increased variably up to 0.10% and 0.10%, respectively, over 36 months at 30°C/65%RH and up to 0.05% and 0.08%, respectively, over 6 months at 40°C/75%RH. Based on these stability results, application of tighter limits at batch release is recommended to ensure a batch released with a content of 'any other impurity' and 'total impurities' at the release limit will remain compliant with the expiry limit throughout the tablets' shelf life.

Response-Tighter limits at batch release is recommended to ensure a batch released with a content of 'any other impurity' and 'total impurities' at the release limit will remain compliant with the expiry limit throughout the tablets' shelf life.

e) Validation of Analytical Parameters:

Query- In relation to the validation of the Product X assay method, related substances method, and dissolution method intermediate precision not provided.

Response- Please provide data demonstrating the intermediate precision of the methods, unless otherwise justified.

Query- Forced degradation studies were conducted to determine the stability-indicating nature of the assay method.

Response- Please provide the results for mass balance of the Assay + Related Substance analytical methods.

f) Stability

Query- Since the proposed finished product specifications include criteria for water content, the stability protocol should be amended to include testing for water content.

Response- Please also provide an assurance that testing for water content will be carried out on the next 3 production batches and the results reported to the TGA.

3. Regulation for filing Drug Product in USA

In the USA, all the food, drugs, cosmetics and medical devices for both humans and animals are regulated under the authority of the United States Food and Drug Administration (USFDA). USFDA acts as public health protector in United States and ensures that all drugs in the market are safe and effective. (5)

New Drug Application (NDA)

For decades, the regulation and control of new drugs in the United States has been based on the New Drug Application (NDA). Since 1938, every new drug has been the subject of an approved NDA before U.S. commercialization. The NDA application is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing in the US. The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA.

The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:

- Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.
- Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.
- Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.

The documentation required in an NDA is supposed to tell the drug's whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged. (6)

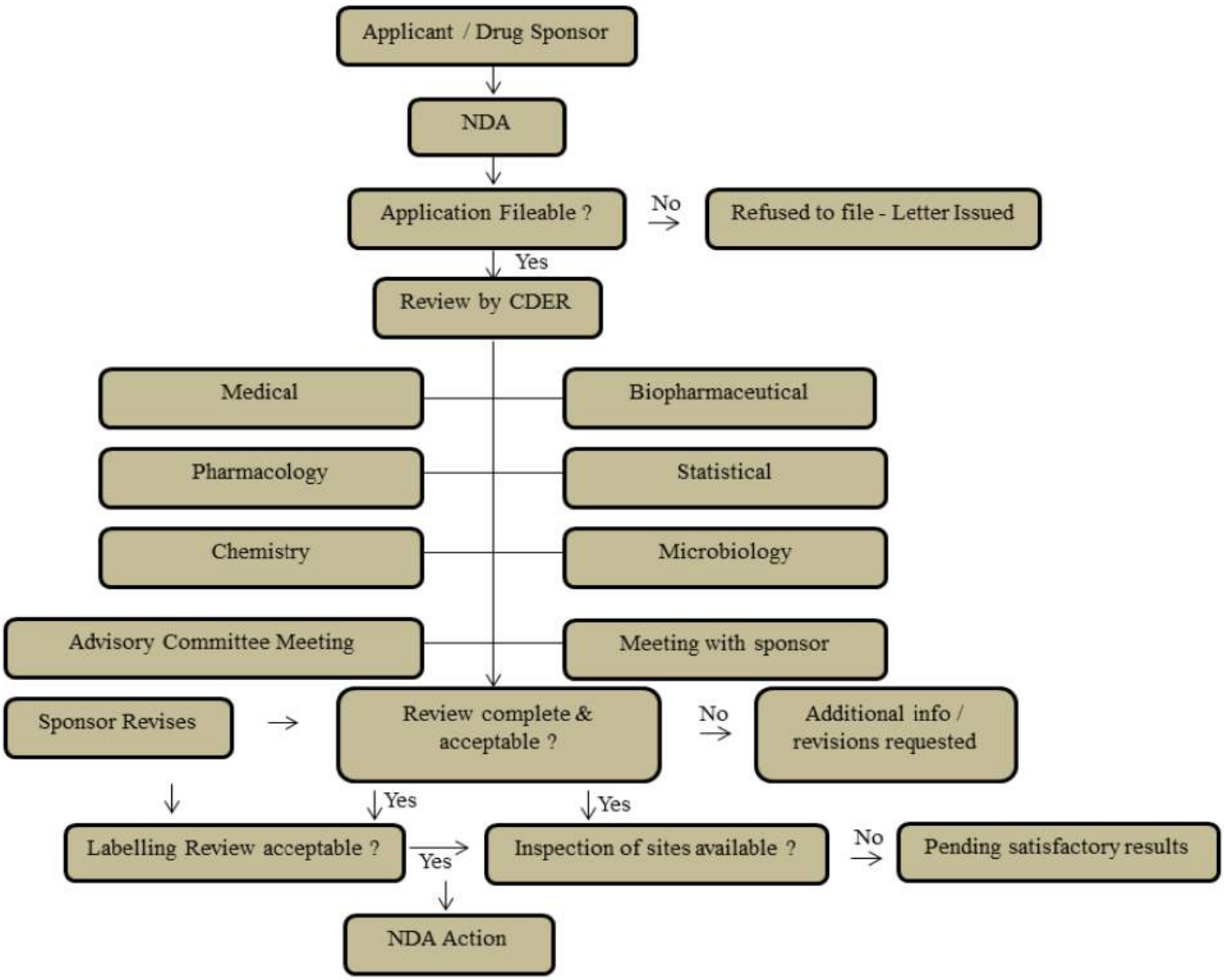


Figure 2. New Drug Application(NDA) (7)

Abbreviated New Drug Application (ANDA): An abbreviated new drug application (ANDA) contains data which is submitted to FDA for the review and potential approval of a generic drug product.

Types of Drug Applications

Type of Drug	Drug Application	Section	Certification	Explanation
Branded	NDA	505 (b)	(1)	New drug includes results of human trials to prove safety and efficacy
			(2)	New dosage form, strength, route of administration, indication of approved drug
Generics	ANDA	505 (j)		Bioequivalent in terms of same active ingredient, dosage, strength, and route
			Para I	Required patent information relating to such patent has not been filed
			Para II	Patent has expired
			Para III	The patent will expire on a particular date
			Para IV	Such patent is invalid or will not be infringed by the drug, for which approval is being sought

Figure 3. Types of drug Application

Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, lower cost alternative to the brand-name drug it references.

A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use. All approved products, both innovator and generic, are listed in FDA's *Approved rug Products with Therapeutic Equivalence Evaluations* (Orange Book).

Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is performs in the same manner as the innovator drug.

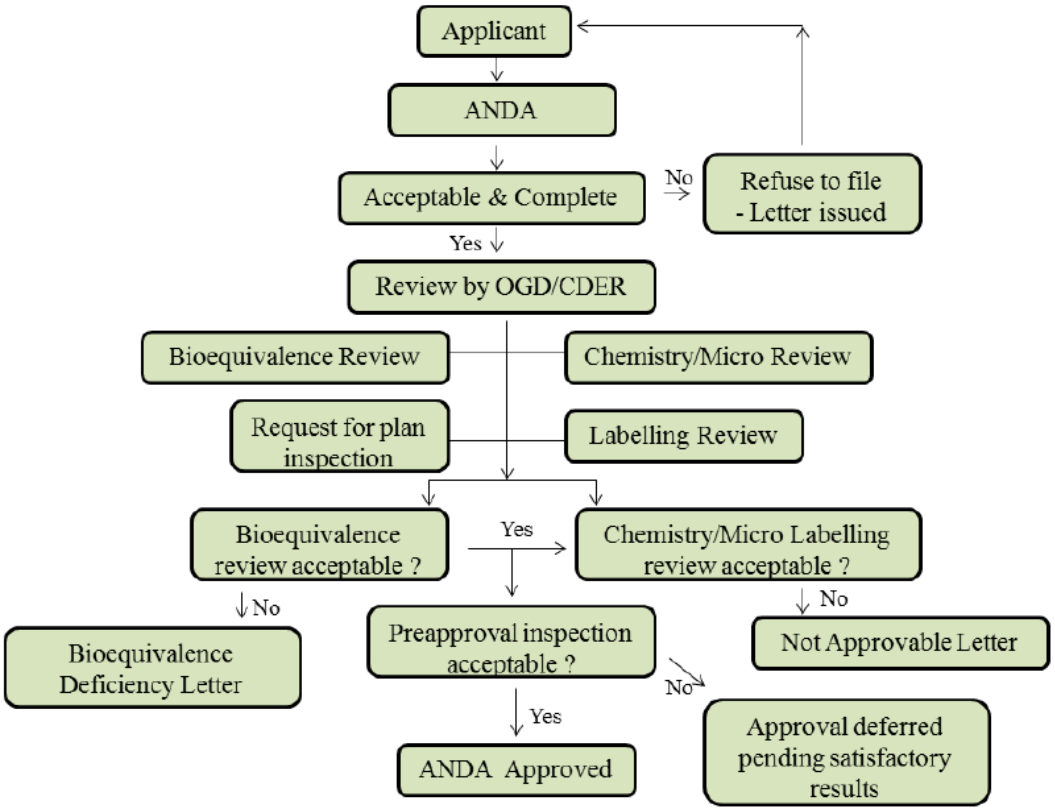


Figure 4. Abbreviated New drug Application (ANDA) (7)

4. Regulation for filing drug product in Europe

The European Medicines Evaluation Agency (EMEA) was established in London, in the year 1995, to coordinate the European Union (EU) member states for evaluating and supervising the medicinal products for both human and veterinary use. It introduced a transparent procedure for the development, consultation, finalization and implementation of pharmaceutical guidelines. The drug approval process in European countries is accomplished in two phases:

1. Clinical trial.

2. Marketing authorization.

A clinical trial application (CTA) is filed to the competent authority of the state to conduct the clinical trial within European Union (EU). The competent authority of that member state evaluates the application. The clinical trials are conducted only after the approval. Marketing authorization application is filed only after all the three phases of clinical trials are completed. The European Legislation containing the pharmaceutical directives has been published in volumes.

In European countries, there are four regulatory procedures: (A) Centralized procedure; (B) Decentralized procedure; (C) National procedure; (D) Mutual recognition procedure.

A. 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).

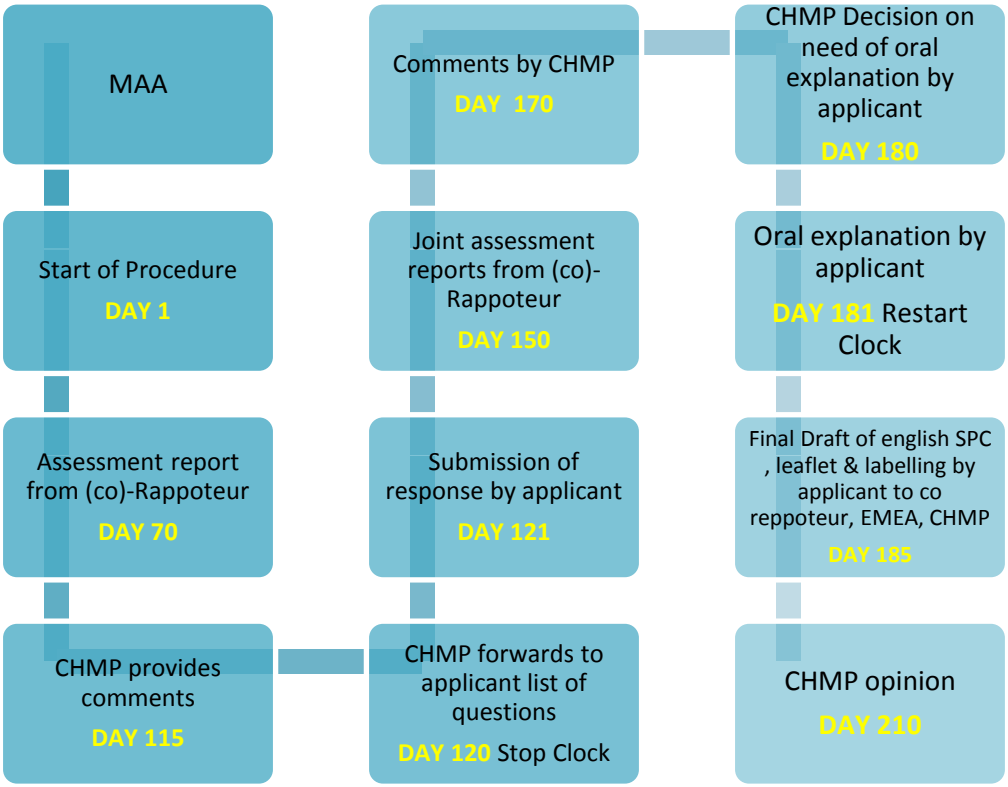


Figure 5. Centralized Procedure (9)

B. 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 EU country and essentially do not fall within the centralized procedure's essential drugs list. (10, 11)
Based on the assessment report which is prepared by the RMS& any comments made by the CMS, MA should be granted in accordance with the decision taken by the RMS & CMS in this decentralized procedure.

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

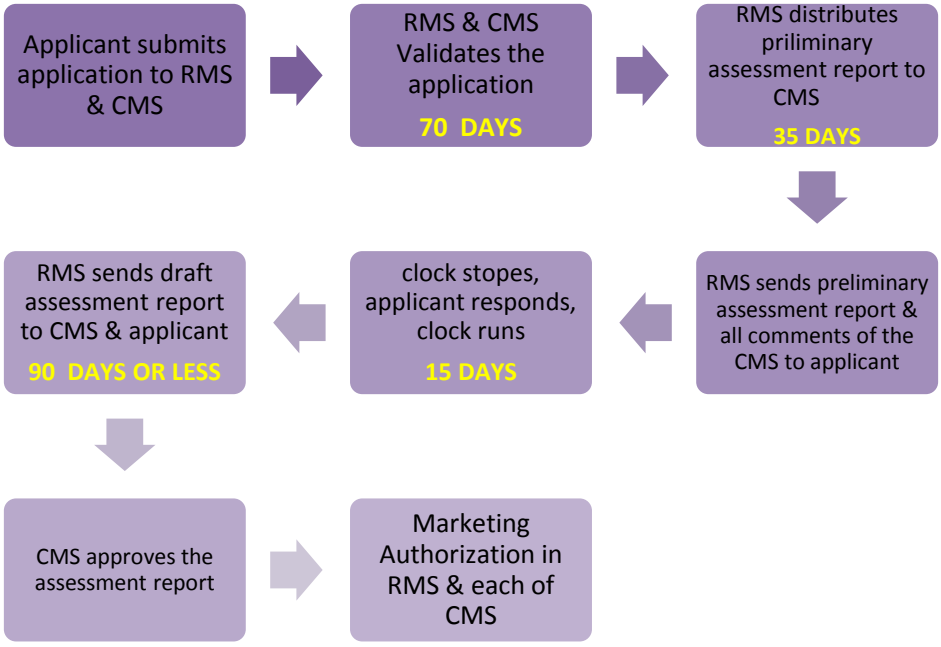


Figure 6. Decentralized Procedure (9)

C. National procedure

The Nationalized procedure is one which allows applicants to obtain a marketing authorization in one member state only. (12, 13)

- 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.

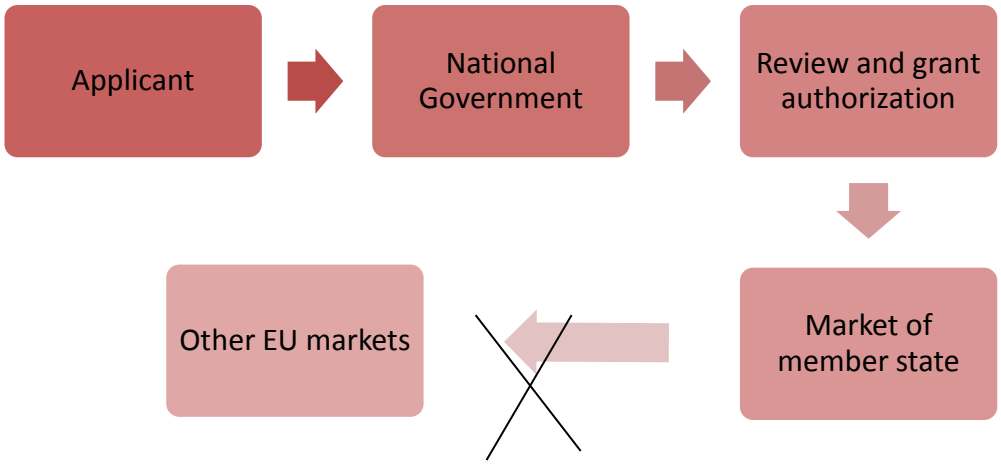


Figure 7. National Procedure (14)

D. 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 previously approved. (15)

- 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.

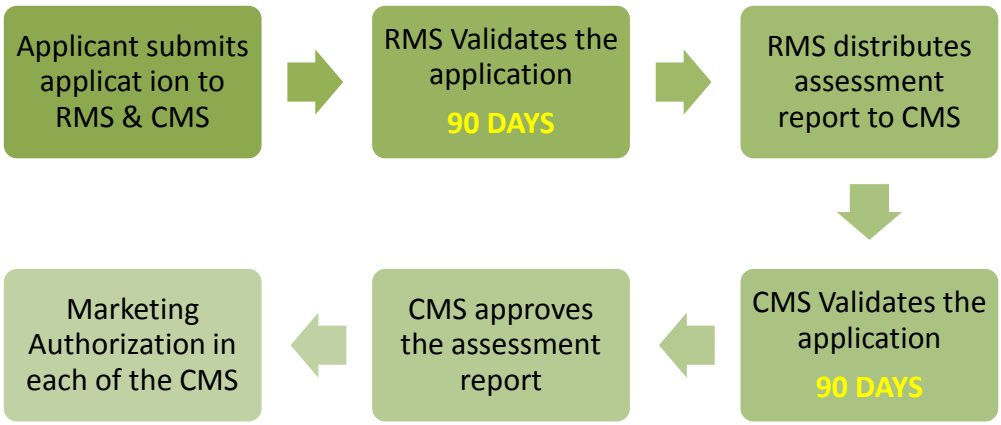
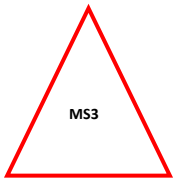
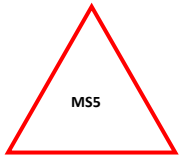
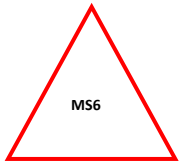


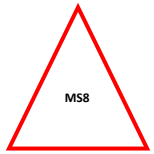
Figure 8. Mutual recognition Procedure (9)

5. Regulation for filing Drug Product in Australia

Table 2 Registration process regulatory phases for NDA Approval Process (16)

Phases	Milestone	Major activities	Sample Timelines		Regulatory requirements
			Activity	**Example of date**	
Pre-submission phase	 Outcome of pre-submission planning sent	• PPF lodged before first of month • Pre-submission planning	• Applicant submits pre-submission planning form • TGA commences processing PPF • TGA *Planning letter* issued	• 31 Oct 2012 • 1 Nov 2012 • On/before 15 Dec 2012	• PPF and attachments lodged via eBS. • Applicants who have lodged complete PPFs will receive *Planning letter* outlining: -submission milestones -any specific conditions for dossier lodgement. -feedback from TGA on justification or other aspects affecting application.
Submission	 Outcome of submission consideration sent	• Dossier arrives at TGA by COB 7th or 14th of month • Processing and considering submission	• Applicant lodged dossier • TGA *Notification letter* issued	• On/before 15 Jan 2013 • On/before 31 Jan 2013	• Applications must be received by TGA by COB 7th or 14th of the month unless otherwise advised in *Planning letter*. • Applicant must certify that all information has been presented at the time of dossier lodgement. Only information requested by TGA in s.31 request or safety related data can be supplied after dossier lodgement. • TGA will process and consider submission dossier against regulatory requirements. Application not provided in accordance with regulatory requirements will be considered not effective and not accepted for evaluation. • Applicant will receive a *Notification letter* advising whether application has been accepted or not for evaluation.

First round assessment	 Outcome of first round assessment sent	• First round assessment • Consolidated section 31 request compiled	• Commencement of evaluation • Consolidation s.31 request sent from TGA to applicant	• 1 Feb 2013 • On/before 31 May 2013	• All dossier content is evaluated during this phase. Draft evaluation reports are prepared. • If required, a consolidated s.31 request for information will be prepared. This includes requests from all evaluation units. This request is compiled in the final month of the phase and sent to the applicant on the date specified in the *Planning letter*.
Consolidated section 31 (s.31) request response	 End of s.31 request response period	• Applicant preparation of response to s.31 request and first round assessment reports • Response received by TGA or response period ends	• 30 day option selected at PPF • 60 day option selected at PPF	• On/before 30 Jun 2013 • On/before 30 Jul 2013	• Applicant nominate in the PPF whether they will respond to the request in 30 or 60 days. The MS3 date is confirmed in *Planning letter*. • If applicant does not respond to a request for information by the date identified in the *Planning letter*, evaluators complete the evaluation based on the information provided in the dossier at dossier lodgement. • Applicant has opportunity to review the first round assessment reports for factual content.
Second round assessment	 Outcome of assessment sent	• Second round assessment	• Completion of second round assessment	• On/before 31 Aug 2013	• Evaluators consider the s.31 response (if applicable) and finalize the evaluation reports. • Where evaluators identify outstanding issues, they will be presented in the evaluation re[orts for consideration by the delegate.
Expert advisory review	 Outcome of	• Delegate overview • Pre-ACPM response and review of reports • Committee papers circulated	Not required in case of Generic medicines	-	• Where the delegate seeks independent advice on aspects of an application, the delegate prepares a request for advice letter. • New innovator products, new indications, and complex application will generally be referred to the ACPM.

	advisory committee sent	• Advisory committee meeting • Committee advice prepared			• Applicant will have an opportunity to prepare a pre-committee response addressing issues raised in the delegate's request for advice letter. • Applicants have an opportunity to review the second round assessment reports for factual content. • Committee advice is finalized and sends to the applicant on the 15th of the month of the meeting.
Decision	 Decision made by delegate	• Delegate decision including PI/CMI/RMP negotiation	• Decision date	• On/before 15 Oct 2013	• The delegate will generally informally advise the applicant of the decision. Formal correspondence of the decision is sent to the applicant. • If the delegate proposes to approve an application, prior to approval, any outstanding issues relating to PI, CMI or RMPs may be negotiated with the applicant. Approval may be conditional on resolution of issues. • If the delegate proposes to reject an application, the reasons for decision are included in the letter of decision, with an explanation of appeal rights.
Post-decision	 Administrative and regulatory activities complete	• AusPAR C-i-C content and PI/CMI requirements fulfilled • Documents published, new /revised ARTG entry	• ARTG entry created	• On/before 15 Nov 2013	• Registration of a new product or variation to a register entry completed. • For applicable application types, a draft Aus PAR will be compiled.
Planned evaluation time is 12.5 months					

6. Result and Discussion

Table 3 Comparative study for USA, Europe, Australia

Requirements	USFDA	EU	TGA
Regulatory authority			
Agency	US FDA	Multiple agencies- • EMEA • CHMP • National Health Agencies	TGA
Number of copies	3	1	1
Application type	ANDA/NDA	MAA	ARTG
Approval timeline	18 months	12 months	15 months
Dossier format	eCTD	eCTD	eCTD and paper
Dossier language	English	English and regional	English
COPP	NA	NA	Legalized required
Registration time	NDA- 8 months ANDA- 10 months	Centralized- 210 days Decentralized- 210 days National- 210 days Mutual Recognition- 180 days	Category 1- 255 days Category 2- 175 days Category 3- 45 days
Registration fees	New drug application- $2,038,100	Marketing authorization application (single	New chemical entity- $45,100

	Generic ANDA- $70,480 Generic finished dosage form(Domestic)- $258,646 Generic finished dosage form(Foreign)- $273,647	pharmaceutical form)- €286,900	New generic product- $17,400
Inspection/Audit	Required	Required	Required Not required in case of OTC products where site is approved from USFDA & EU GMP.
Registration process	One registration process NDA & ANDA	Multiple registration process- • Centralized(European Community) • Decentralized(At least 2 member states) • Mutual Recognition(At least 2 member states) • National(1 member state)	Multiple registration process- • Category 1 • Category 2 • Category 3
Changes in approved drug can be done by filing	• Annual Report • CBE-0 • CBE-30 • PAS- Prior Approval Supplement (17)	• Type IA Variation • Type IB Variation • Type II Variation	Variations to prescription medicines • Corrections, notifications and quality information changes • Product information(PI) changes
CTD Module 1			
TSE/BSE study	Data not required	Data required	Data required
Braille code on labeling	Not required	Required	Not necessarily required
Field copy certificate	Required	Not required	Not required
Patent certificate	Required	Not required	Required
Debarment certificate	Required	Not required	Not required
Mock up	Not required	Required	Not required

Letter of Authorization	Required	Not required	Not necessarily required
Pharmacovigilance system study	Not required	Required	Required
Label mock up	Not required	Required	Required
Risk management plan	Required	Required	Not required
Manufacturing and Control			
Number of batches for Mfg	3 Pilot scale (One can be smaller if justified)	3 Pilot scale (One can be smaller if justified)	3 Pilot scale (One can be smaller if justified)
Manufacturing license	Required	Required	Required
Packaging	A minimum of 1,00,000 units	Not required	Required
Process validation	Required	Required	Required
Batch size	Minimum of 1,00,000 units	Minimum of 1,00,000 units	Minimum of 1,00,000 units
Stability			
Stability zone	Zone II / IV a	Zone II / IV a	Zone II / IV a
Number of batches for stability	3 Exhibit batches	3 Exhibit batches	3 Exhibit batches
Stability guidelines reference	ICH Q1A (R2)	ICH Q1A (R2)	ICH Q1A (R2)
Condition	Long term 25°C ± 2°C/60% RH ± 5% RH/30°C ± 2°C/65% RH ± 5% RH Accelerated 40°C ± 2°C/75% RH ± 5% RH	Long term 25°C ± 2°C/60% RH ± 5% RH/30°C ± 2°C/65% RH ± 5% RH Accelerated 40°C ± 2°C/75% RH ± 5% RH	Long term 25°C ± 2°C/60% RH ± 5% RH/30°C ± 2°C/65% RH ± 5% RH Accelerated 40°C ± 2°C/75% RH ± 5% RH
Date and time of submission	6 months accelerated & 6 months long term	6 months accelerated &12 months long term	6 months accelerated & 12 months long term

Container orientation	Inverted & upright	Do not address	Inverted
Clause	21 CFR part 210 & 211	Vol4 EU Guidelines for medicinal products	Australian regulatory guideline EUs for prescription medicines appendix 14: Stability testing
QP Certification	Not required	Required	Not required
Clinical/BA/BE Study			
Number of subjects for BE studies	Should not be less than 12	Should not be less than 12	Should not be less than 12
Age	18 years of age or above	18 years of age or above	18-55 years of age (18)
Sex	• Male and female subjects both should be enrolled in BA and BE • In case of oral contraceptives, it is to be evaluated in female subjects because the indication is specific to females. • If a drug has the potential to be a teratogen, the drug product should be evaluated in male subjects (20)	Subjects could belong to either sex; however, risk to women of childbearing potential should be considered. (19)	Subject could belong to either sex.
Fed/Fasting	Conducted under fasting conditions (after an overnight fast of at least 10 hours) except when tolerability issues are anticipated with fasting. In these cases, we recommend that applicants conduct only a fed study	A bioequivalence study should be conducted under fasting conditions as this is considered to be the most sensitive condition to detect a potential difference between formulations	A bioequivalence study should be conducted under fasting conditions as this is considered to be the most sensitive condition to detect a potential difference between formulations
Clinical study design	Randomized, Crossover design	Crossover design	Non-replicated, randomized, crossover design.
CRO	Audited by FDA	Audited by EMEA	Audited by TGA

7. Conclusion

Drug approval process is generally composed of 2 steps: Clinical Trial Application and Application for Marketing Authorization of drug to the Regulatory Authority. Information regarding Quality, Safety and Efficacy of the drug is almost similar in all countries which is to be submitted to Regulatory Authority. But apart from this information, registration time, registration fees, and clinical trial review process is different. ICH has taken many steps for Harmonisation. ICH developed CTD guidelines for US, EU and Japan. This will minimize the duplication of work which is to be carried out in Research and Development of the new drug, as ICH or WHO drug approval process is initiated at wider global level.

The primary aim of regulation of drug products in Australia, US and Europe is regarding the public health. There are various regulations for the development of the drug, its manufacture, trial and testing, so that they are safe for human use.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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