



"GENERIC DRUG DEVELOPMENT IN THE USA, EUROPE AND MEXICO WITH HARMONIZATION – A REGULATORY INSIGHT"

INTRODUCTION

The pharmaceutical industry is the most regulated. To protect the health and wellbeing of the public, the government has enforced various rules and regulations. It is the responsibility of regulatory affairs to ensure efficacy, safety, and quality of medicines in the entire product lifecycle and is expected to carry out its tasks without bias. There is a dual role in regulatory affairs. One is to develop and execute a regulatory strategy to ensure that the collective efforts of the drug development team result in a product that is approvable by global regulators but is also differentiated from the competition in some way. The other role is to ensure that the company's activities are carried out as per the set guidelines by the regulatory authorities. This broad area covers the activities starting in the non-clinical laboratories, and ongoing throughout the entire clinical development phase, marketing, and lifecycle of a product.

A Generic drug is "a drug product which is comparable to a reference (brand) listed drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use". The decreased cost of generic drugs is the attraction to the customer which leads to the increased use of generic drugs. A generic version of the brand/innovator drug product is brought to the market by the generic drug companies at a lower price, which benefits the public and makes healthcare affordable. The process of bringing a generic version into the market is not as simple as just copying the brand-name product. Certain studies are also required by the generic companies to conduct and also pass the strict standards laid by the regulatory agencies. More of the population lives in the regions with emerging markets and the real economic growth comes from this region. This results in MNC's approach toward these emerging markets which include RUSSIA, INDIA, CHINA, MEXICO, KOREA, etc.

BACKGROUND

The health systems in the USA, Europe, and Japan have developed rapidly since product authorization systems were established in the mid of the last century (the USA since the 1930s, Japan since the 1950s most European countries since the 1960s). While an increasing number of national laws, regulations, other legislative documents, and guidelines have been issued, the industry has expanded into international markets, facing different requirements in different countries. The health system in the USA was developed in the 1930s as described above. The requirement to develop Harmonisation in Europe started in the mid of the 1960s (65/65/EEC), setting up some basic requirements for medicinal products. However, increasing emphasis has only been put on harmonization in Europe since the 1980s to tackle the problems caused by different requirements in different countries. The health system in Mexico was developed quite later as compared to the other regions mentioned above. It was developed in the year 2001. Before that, the regulations were not as stringent as required. During the 1980s as well, discussions between Europe, the USA, and Japan on harmonization in these three regions started. Resulting of these discussions, the ICH (International Conference on Harmonisation) was established in 1990. Since then, many steps have been made towards harmonization of the requirements for medicinal products in Europe, the USA, and Japan through the ICH process. However, there are still quite some differences between these three regions that have to be taken into consideration when developing a dossier intended to be suitable for all regions.

In parallel to the development of the health systems and the regulatory requirements, an increasing number of medicinal products have been authorized and marketed. Along with this, an increasing focus has been put on the price of medicinal products to be reimbursed by the different national health systems. In addition, emphasis has been placed on reducing animal experiments and clinical trials on humans to a minimum for ensuring the safety and efficacy of a medicinal product. Resulting from this development, the generic industry was born, referring to pre-clinical (pharmacological and toxicological) tests and clinical trials conducted by the innovator and hence being able to offer medicinal products at a lower price.

METHODOLOGY

Regulatory Authorities

The regulatory authorities are the authorities who play a double role in the development of safe and effective medicines and make them available to the public. The First role of regulatory authority is to develop strategies and guidelines which can be used by the Industries while developing Drugs. And the other role is to check whether the regulations framed are followed by the industries. The role of the regulatory authority doesn't end here. It plays a big role in various other endeavors.

USA:

The regulatory authority of the USA is the Food and Drug Administration. Also known as the United States Food and Drug Administration. It was formed in 1906 and till then it regulates drugs and other supplementary products in the USA. The regulations passed by the USFDA are from FD and C act which has various sections

in it. Also, regulations and Guidelines are developed in the Code of Federal Regulations (CFR) chapter 21, which provides guidelines and regulations which are to be followed by the industry.

Europe:

The regulatory authority of Europe is not a single regulatory body. There are various regulatory authorities in Europe for the regulation of medicines in Europe. The Agencies are the European Commission (EC), European Medicines Agency (EMA), Heads of Medicines Agencies (HMA), European Directorate for the Quality of Medicines (EDQM), and National Competent Authorities. The Bodies collectively look after the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use.

Mexico:

The regulatory authority of Mexico is COFEPRIS which is known as Federal Commission for the Protection against Sanitary Risks. It is the authority with competence to control and regulate drug products in Mexico. The COFEPRIS is in charge of food and drink, tobacco products, and other healthcare supplies (medical equipment, vaccinations, blood, tissues, etc.) in addition to drug items. All of these goods and industries together account for almost 10% of Mexico's GDP and a 92 billion USD market. Production, distribution, marketing, imports and exports, advertising, sales, supply, and other associated activities are all under the control of COFEPRIS. The World Health Organization named COFEPRIS as the National Regulatory Authority of Regional Reference of pharmaceuticals and biological products in July 2012 through the Pan American Health Organization.

How to Get Started:

Before a dossier for a generic human medicinal product can be developed for concerning regions, or transferred from one region to the other, some basic pre-requisites need to be fulfilled and some issues to be taken into consideration to ensure successful development. This is also important and concerning the expected timeline of the development as well as the expected costs. Some of these issues are important to check whether the project is feasible at all. Others are important for the calculation of the required time and the costs and hence for the decision whether to follow this way or choose another, e.g. whether to in-license a generic US dossier and adapt it for a European submission or to newly develop a generic dossier for Europe.

The following list of questions should be checked:

Reference Products

1. Are the same medicinal products (reference products) with the same active pharmaceutical ingredient(s) in the same strength(s) and the same dosage form(s) with the same route of administration authorized and marketed in the USA, Europe and the Mexico respectively have they been authorized and marketed?
2. Is the qualitative composition of the reference medicinal product the same in all regions?
3. Are there any hints leading to the manufacturing sites of the US and/or the Europe product?

4. Is the same API used in all regions for the reference medicinal product (e.g. polymorphic form, enantiomeric form, salt)? If not, are there any relevant differences between the different forms that are used?
5. Is a comparative dissolution profile of the reference products in all regions available? Are the dissolution profiles of the reference products comparable?

Protection Period of the Reference Products

1. Are there any valid patents in one or all target regions that would need to be circumvented or challenged, e.g., some process patent for the API or a formulation patent for the finished dosage form that makes a different formulation necessary?
2. When does the data exclusivity expire in the USA, Europe, and Mexico, or has it expired already?
3. Is there any additional protection valid in one or all regions?
4. Can the applicant benefit from a "first to file" regulation in the USA?

Manufacturers of API and Finished Product

1. Is it planned to use the same production site for the European market, Mexican market, and the USA market or is a transfer to a second manufacturing site necessary or preferred?
2. Has the API manufacturer been audited for GMP compliance (EU/USA)?
3. Is the finished dosage form developer and manufacturer suitable for all regions, i.e., GMP certified by the EU and US agencies?

Manufacturers of API and Finished Product

Having clarified the basic issues concerning reference products and assuring that the development of a generic product for all regions is feasible, the manufacturers should be looked at.

Dependent on the specific project, the following situations are possible:

- Development of a new generic product for both regions with the identical manufacturing sites
- Development of a new generic product for both regions with different manufacturing sites
- Transfer of an existing dossier from one region to the other while maintaining the manufacturing sites
- Transfer of an existing dossier from one region to the other while also transferring the production to another manufacturing site

The decision for one or more manufacturers should be made concerning the suitability, time, and cost. The suitability of a manufacturer comprises his know-how, reliability, and availability as well as whether the site conforms to GMP requirements in Europe and the USA and is assessed positively by the authorities. Mexico allows the site inspected and verified by the US or Europe. Time and cost should be calculated concerning the development or transfer itself as well as the running cost once the product is on the market (e.g., production cost, shipping cost). Additionally, the status of patents should be considered. If a patent is still valid, it might

be an advantage to have an additional manufacturing site in a patent-free country for the launch batches. This would enable the generic company to enter the market as soon as the patent expires, i.e., to win or at least not to lose a few days compared to competitors.

Dossier Format

The format for the dossier to be submitted to gain market approval from the regulatory body should be as per the regulatory requirements of the concerned regulatory authority. Each country has its content and requirement which is to be followed by the applicant to avoid query and delay in getting approval. The USA and Europe follow the CTD format while Mexico has its Country specific Application Dossier Requirements.

The CTD format was developed by the International Conference on Harmonization (ICH) in an attempt to streamline the variability of submission requirements among Japan, the European Union, and the United States. The CTD collates quality, safety, and efficacy information into a common format that has been adopted by ICH regulatory authorities.

Only ANDA and Marketing Authorization application submissions made electronically, following the eCTD format on the date of submission will be subject to the review in the case of the USA and Europe. For Europe also NeeS is accepted.

For Mexico, the format used to prepare an Application Dossier is not as per CTD. Mexico has its country-specific guidelines and format for the submission of the dossier which is later described in this document.

CTD Format:

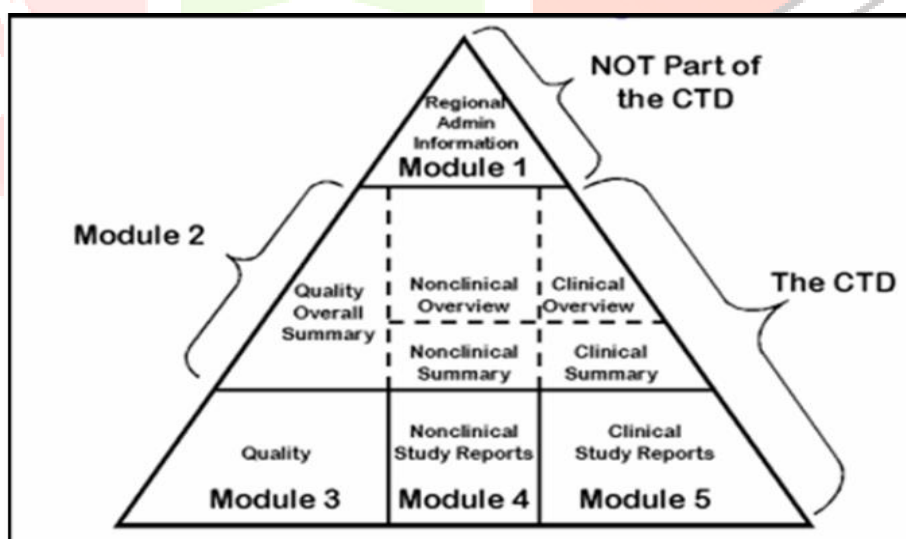


Figure – 1 CTD Triangle

As shown in the above figure, the CTD format consists of the following 5 different Modules:

- Module 1. Administrative Information and Prescribing Information
- Module 2. CTD Summaries
- Module 3. Quality

- Module 4. Nonclinical Study Reports
- Module 5. Clinical Study Reports

Marketing Authorization Procedure

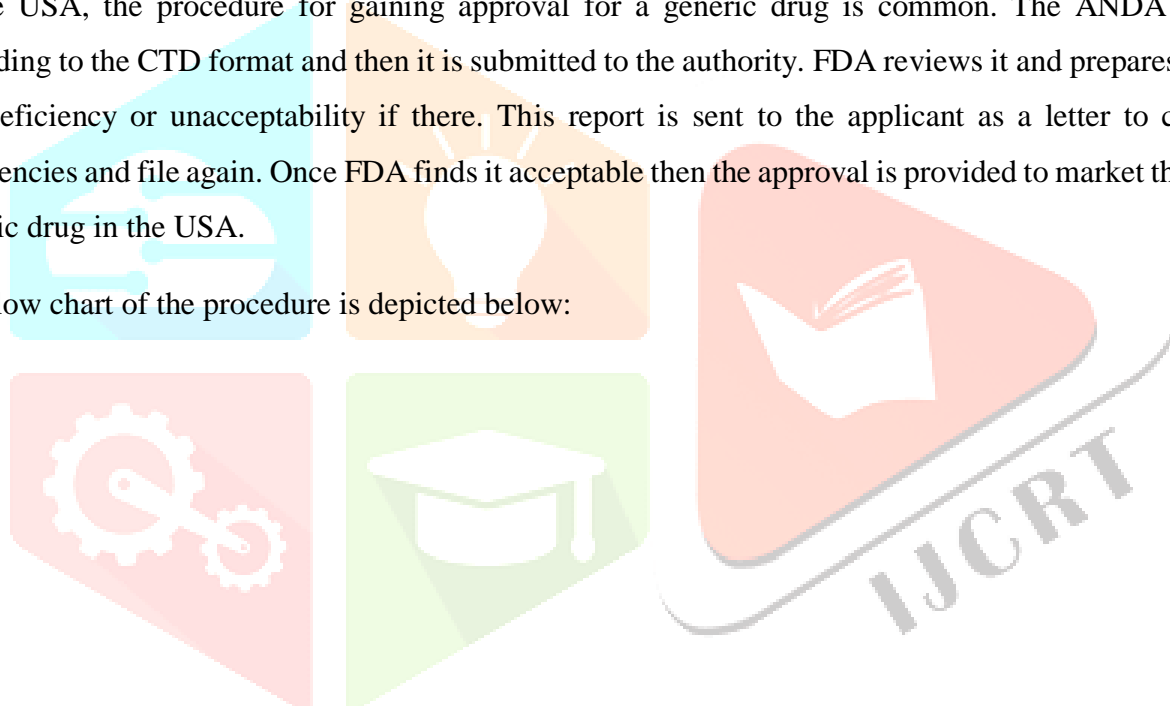
A generic medicinal product can only be marketed once it has received approval from the competent authority to market it in their market. For this, the application is to be filled i.e. the dossier is to be submitted to the authority which reviews it, and later if found acceptable, the authorization to market the drug in their market is provided by the authority. Only then the generic drug can come to the market.

All nations have a different procedure for filling and reviewing the application. The Industry is required to follow the procedure and stay abide by the requirements.

USA:

In the USA, the procedure for gaining approval for a generic drug is common. The ANDA is prepared according to the CTD format and then it is submitted to the authority. FDA reviews it and prepares a report for any deficiency or unacceptability if there. This report is sent to the applicant as a letter to correct these deficiencies and file again. Once FDA finds it acceptable then the approval is provided to market the developed generic drug in the USA.

The flow chart of the procedure is depicted below:



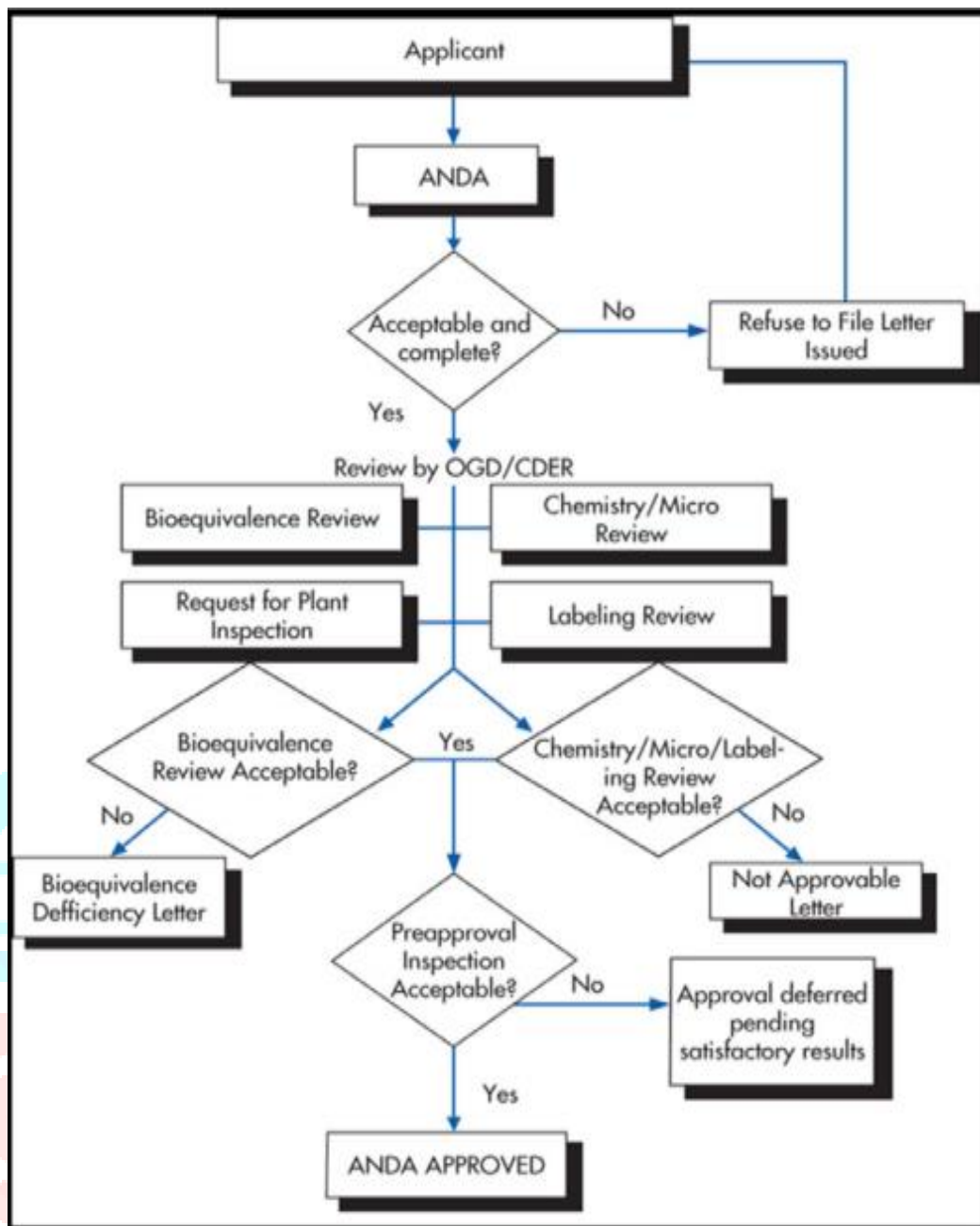


Figure – 2 ANDA Review Process

Europe:

A medicinal product can only be placed on the market in Europe when a marketing authorization is granted by the competent authority of a member state for its nation or when granted by following Regulation (EC) No 726/2004 for the entire Union. The marketing authorization holder must be established within Europe.

The four described procedures are published by the EC in consultation with the competent authorities of the member states, EMA, and interested parties.

- Centralized Procedure (CP)
- Decentralized Procedure (DCP)
- Mutual Recognition Procedure (MRP)
- National Procedure (NP)

Centralized Procedure (CP):

A marketing authorization granted under the centralized procedure is valid for the entire community market, which means the medicinal product may be put on the market in all member states.

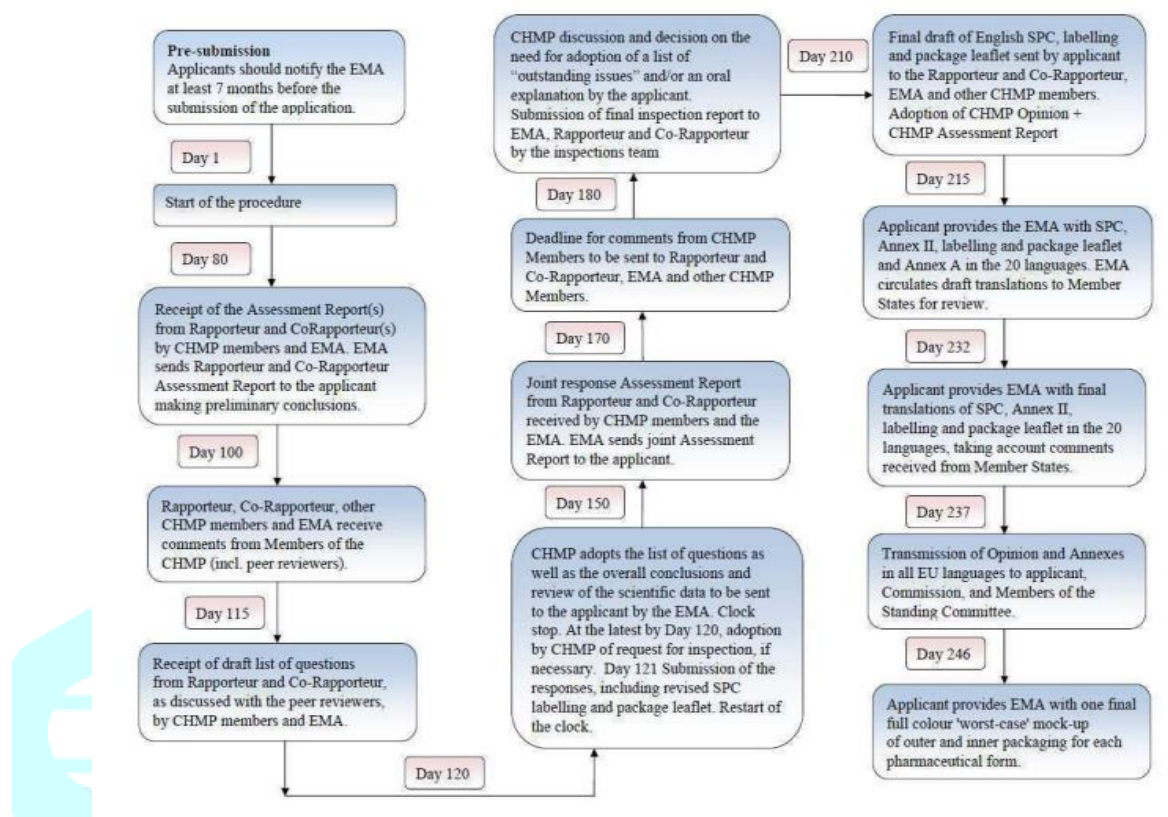


Figure – 3 Centralized Procedure

Decentralized Procedure (DCP):

The DCP is to be used to obtain marketing authorizations in several MSs where the medicinal product in question has not yet received marketing authorization in any Member State at the time of application. The procedure to be followed will depend upon whether it is an MS or the MAH which initiates the DCP. As set out in Directive 2001/83/EC MSs have to approve during the DCP, the assessment report, SmPC, the package leaflet, and the label.

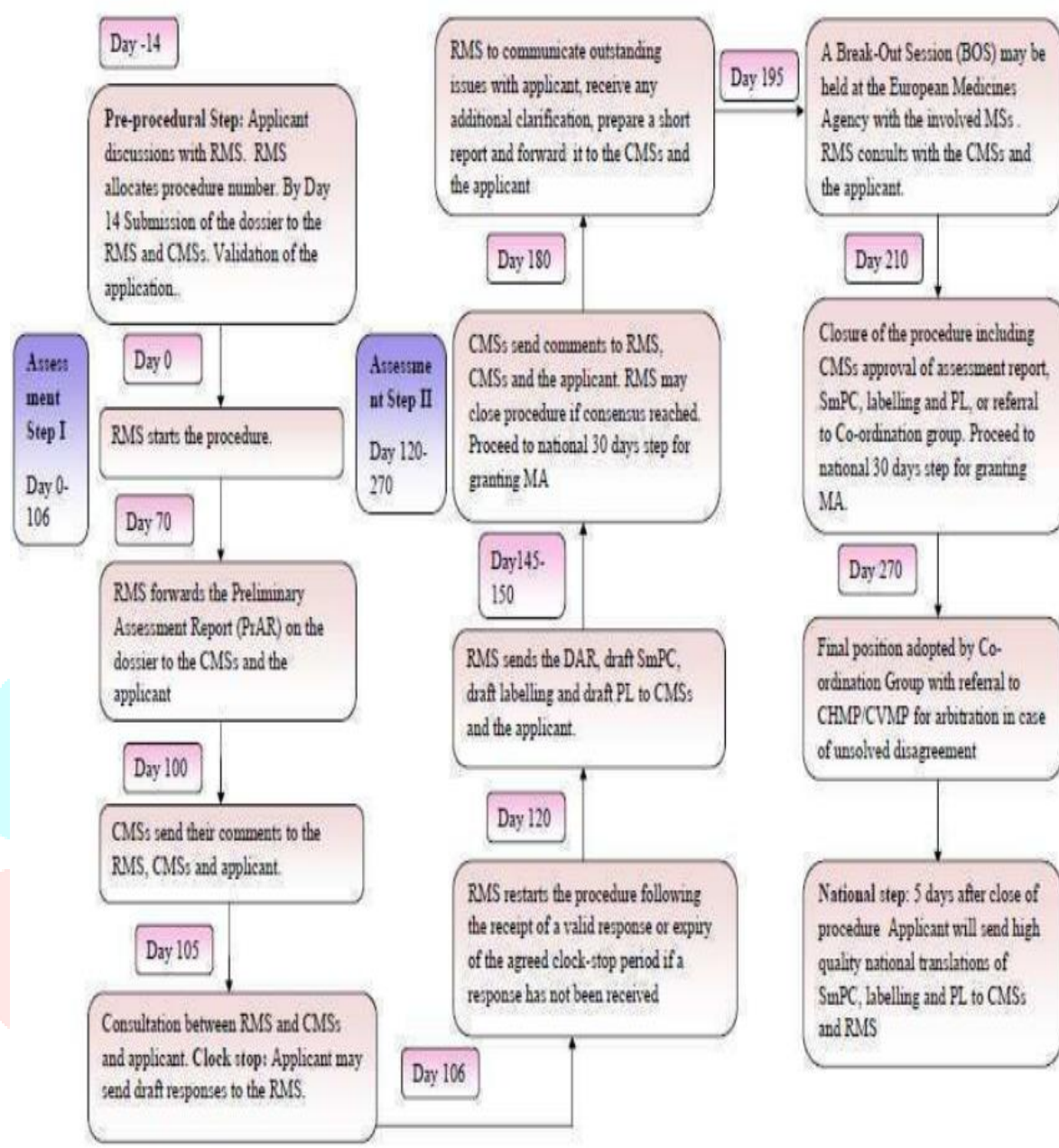


Figure – 4 Decentralized Procedure

Mutual Recognition Procedure (MRP):

The MRP is to be used to obtain marketing authorizations in several MSs where the medicinal product in question has received marketing authorization in any MS at the time of application. The procedure to be followed will depend upon whether it is an MS who triggers or the MAH who initiates the mutual recognition

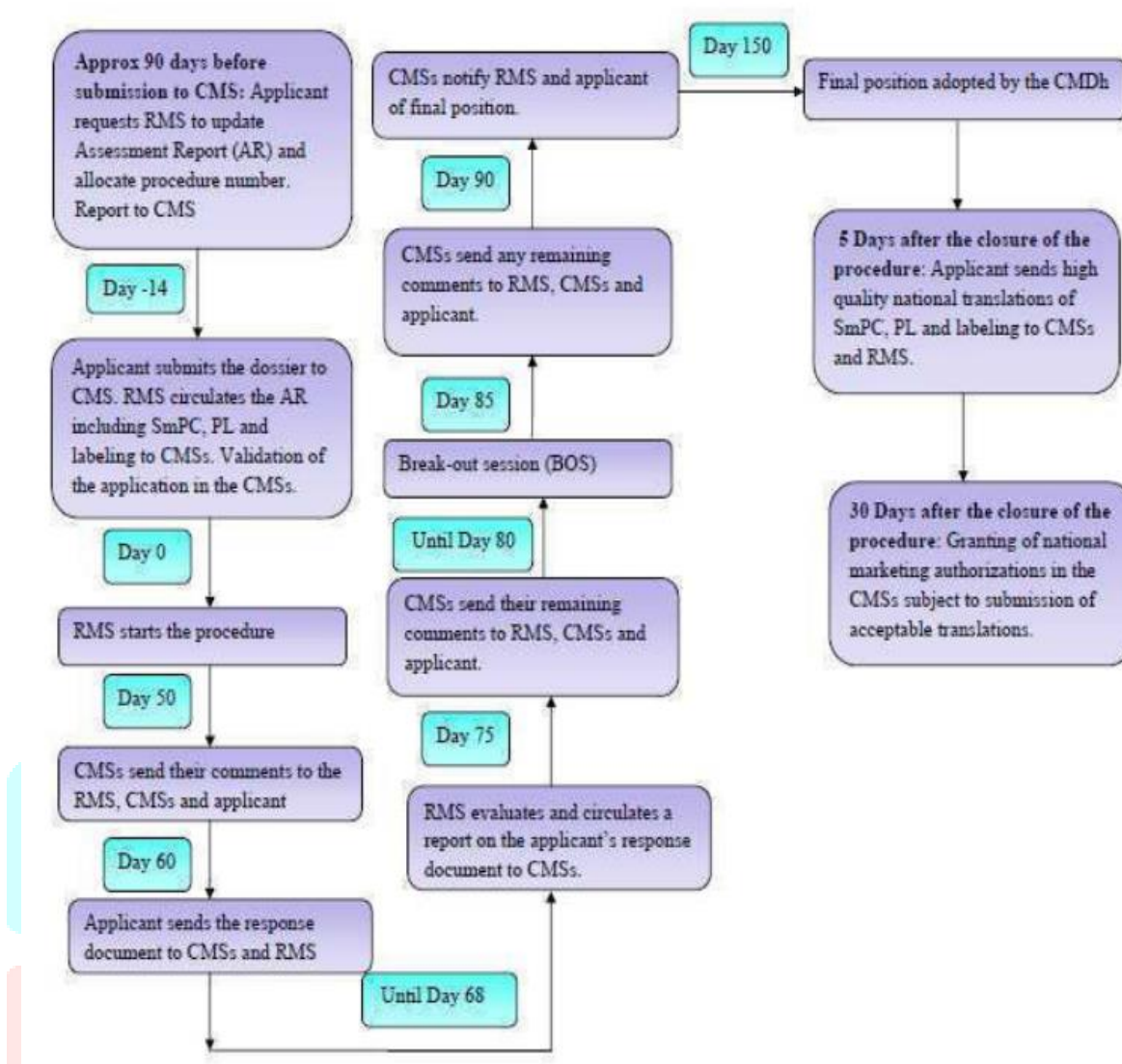


Figure – 5 Mutual Recognition Procedure

National Procedure (NP):

Independent national procedures will continue but are strictly limited to medicinal products which are not to be authorized in more than one Member State.

In addition, as provided for in Article 30(2) of Directive 2001/83/EC, harmonization of authorizations for medicinal products authorized in the Union is to be promoted via a coordinated approach for referring medicinal products, for which divergent decisions have been adopted, to the EMA and the CHMP.

NP can also be used for extensions of authorized medicinal products as far as no prior harmonization has been achieved for the initial marketing authorization. The competent authorities of the MSs are responsible for granting marketing authorizations for medicinal products, which are placed on their markets, except for medicinal products which are authorized under Regulation (EC) No 726/2004 which may only be authorized via the CP (mandatory scope).

The NP is the preliminary stage for the MRP and DCP. To obtain a national marketing authorization, an applicant must apply to the competent authority of only one MS.

When the marketing authorization is issued nationally, it is valid only in that country where it has been issued and can be placed on the market only in that country.

MEXICO:

Mexico also has a common Procedure applied to gain market approval for a generic drug. Unlike Europe which has different procedures, Mexico does not have different procedures.

For Mexico, the dossier is to be submitted in the local language i.e., Spanish. This is the biggest barrier in the case of developing a dossier for Mexico in a Country whose local language is not Spanish. Also, there is a special requirement for Mexico which states that the BE study for the generic drugs should be performed in Mexico.

Hence authorization requires a third party in Mexico. The dossier is prepared in the English language as specified in the requirement. Module 1 and module 2 are prepared in the country of origin. These two modules are provided to the third party in Mexico, which prepares module 3 and converts the whole dossier into the Spanish language and submits it to COFEPRIS for review.

These are the procedures that are followed by the applicant in case to obtain market approval for the generic drugs in the USA, Europe, and Mexico.

Conclusion

The development of generic Drugs is not an easy task at all. Various pre-requisites are a challenge that should be kept in mind while developing a Generic Drug. As the development, the preparation of the Dossiers for market approval application is also difficult and time-consuming.

Thus, Harmonization is a way to save time and cost for the same Generic Drug to be marketed in different regions. Keeping in mind the requirements of each region, a dossier must be developed which can further be transferred to another region after getting a marketing authorization in one region. But this transferring of the dossier is also not feasible in all regions. In that case, only the development of the new Dossier is the option.

Transferring the dossier of a generic oral human medicinal product from the USA to Europe or vice versa seems at first glance like an easy, quick, and low-cost opportunity that should be taken. However, as in most cases, things aren't as easy as they seem. Several factors need to be considered and checked as they influence feasibility, time, and cost. For some cases, a dossier transfer is not possible, for others a new development for the target region is the better way to go.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none

REFERENCES:

1. Jaime R. Hornecker, PharmD, BCPS, Generic Drugs: History, Approval Process, and Current Challenges (accessed on 5th Jan 2015) <http://www.uspharmacist.com/content/s/78/c/13785>
2. The effect of generic competition on the price of brand-name drugs; Joel Lexchin
3. New product development process and time-to-market in the generic pharmaceutical industry; Janez Prašnikar, Tina Škerlj
4. The differences between the branded and generic medicines using solid dosage forms: Invitro dissolution testing; Mubarak Nasser Al Ameri, Nanda Nayuni, K.G. Anil Kumar, David Perrett, Arthur Tucker, Atholl Johnston
5. A comparative analysis of generics markets in five European countries; Livio Garattini, Fabrizio Tediosi
6. International Conference on harmonization, Process of harmonization <http://www.ich.org/about/process-of-harmonisation.html>
7. International Conference on harmonization guidelines: Quality, Safety, Efficacy, Multidisciplinary <http://www.ich.org/products/guidelines>
8. European Medicines Agency official website <http://www.ema.europa.eu/ema>
9. The United States Food and Drug Administration- Official website <http://www.fda.gov/Drugs/default.htm>
10. EudraLex - Volume 2 - Pharmaceutical Legislation Notice to applicants and regulatory guidelines medicinal products for human use European Medicines Agency official website www.ema.europa.eu, via the index "Regulatory"
11. Heads of Medicines Agencies- Co-ordination group for Mutual recognition and Decentralized procedure (human) www.hma.eu/cmdh.html
12. Regulatory information by FDA <http://www.fda.gov/RegulatoryInformation/default.htm>
13. Office of generic drug- the centre of drug evaluation and research <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm>
14. Heads of Medicines Agencies <http://www.hma.eu/human.html>
15. Directive 2001/83/EC on the Community code relating to medicinal products for human use Directive 2001/83/EC as amended, Article 10(1)
16. The applicant shall not be required to provide the results of toxicological and pharmacological tests or the results of clinical trials Directive 2001/83/EC as amended, Article 10(1) and (2)(a)
17. Directive 2001/83/EC, not amended, Article 10(1)(a)(iii); Eudralex Volume 2A Chapter 1 section 6.
18. Regulation EC/141/2000, Article 8 and Regulation EC/847/2000.
19. Commission Regulation (EC) No 1982/2004 of 18 November 2004 implementing Regulation (EC) No 638/2004 of the European Parliament and the Council on Community statistics relating to the trading of goods between the Member States and repealing Commission Regulations (EC) No 1901/2000 and (EEC) No 3590/92 Regulation EC/1901/2000, Article 36 (5).

20. Regulation EC/1901/2000, Article 37.
21. Regulation EC/1901/2000, Article 38.
22. Directive 2001/83/EC as amended, Article 6.
23. Agreement On Mutual Recognition Between The United States Of America And The European Community www.mac.doc.gov/mra/mra.htm
24. Memoranda of Understanding and Other Cooperative Arrangements www.fda.gov/InternationalPrograms/Agreements/MemorandaofUnderstanding
25. Regulatory Procedures Manual www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm
26. Food and Drug Administration. FDA Announces Fiscal Year 2015 Generic Drug User Fee Rates.
27. Reddy, K. S. (2011, 5-6). CTD Dossier Preparation. Retrieved 7-12, 2014, from Pharmexil: <http://www.pharmexcil.com>
28. . Fees are payable to the European Medicines Agency. European Medicines Agency. [Online]

