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Review Article

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Product Life Cycle Management in Europe: A Review

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Abstract

This review article helps to study the practical aspects of different phases of life cycle of pharmaceutical products including sterile and non-sterile dosage forms in regulated market of Europe, to study the European standards and their requirements for new registration of injectable drugs, to study the product life cycle start from the product identification by market surveying and till its withdrawal or renewal in the Europe market, the data may contain official information to be taken from the EMEA guidelines, prepare, compile and submit the regulatory data according to the eCTD format to the regulatory agencies of Europe as critical phase of life cycle. The pharmaceutical industry is today conceivably the most highly regulated of all industries demanding a high level of information to be submitted to governments before a pharmaceutical product is brought to the marketplace. Each country holds different regulatory department. In this scenario, the product life cycle management in regulated market of Europe sustains a significant value. (1-2)

Keywords: Regulatory affairs, European standards, EMEA Guidelines, eCTD, Marketing Authorization, Product life-cycle management (PLM)

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1. Introduction

Regulatory affairs called as Government affairs, is a professional with in regulated industries such as pharmaceuticals, biotechnology, medical device research and development industries are among the most highly regulated industries all over the world. The pharmaceutical industries were becoming throughout the world are moving ahead towards becoming more and more competitive.

Regulatory Affairs does not have a single definition. It is the "act of gathering and analysing regulatory information and monitoring the current regulatory climate". However, it is more than gathering information to generate regulatory strategies and gain a competitive advantage for obtaining regulatory approvals. It is also defined as understanding the pharmaceutical rules and regulations knowing how the regulations are applied and experienced and applying the regulatory knowledge to specific circumstances.

Regulatory affairs in pharmaceutical industry to aim in the protection of human health. Current regulation endorses numerous activities to ensure safety, efficacy, and quality of drug products. All the pharmaceutical products are invented, designed, and tested by medical researchers and other specialists and make sure it receives country specific health authority's approval. Some of the organizations working as drug regulatory authorities worldwide are given below:

Health Authority

The EMEA is a decentralized body of the European Union with headquarters in Amsterdam, Netherlands. It is main responsible in the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. The EMEA is responsible for the scientific evaluation of applications for European marketing authorization for medical products (centralized procedure). Under the centralized procedure, companies submit a single marketing authorization application to EMEA. The safety of medicines is monitored constantly by the agency through a pharmacovigilance network. The EMEA takes appropriate actions if adverse drugs report suggests changes to the benefit-risk balance of a medicinal product.

Drug approval process: A Sponsor has multiple possibilities when seeking approval to market a new drug in European countries. Below are the steps how a new product launched into the market.

Table 1. Health Authorities (1-2)

Country Name	Health Authority	HA Short Form
United States	Food and Drug Administration	FDA
Australia	Therapeutic Goods Authority	TGA
Canada	Therapeutic Product Directorate	TPD
Europe	European Medicine Agency	EMEA
Brazil	Agencia Nacional Vigilancia Sanitaria	ANVISA
United Kingdom	Medicines and Healthcare products of Regulatory Agency	MHRA
Japan	Ministry of Health and Labour Welfare	MHLW
South Africa	South African Health Products Regulatory Authority	SAHPRA
Singapore	Health Science Authority	HAS
India	Drug Controller General of India	DCGI

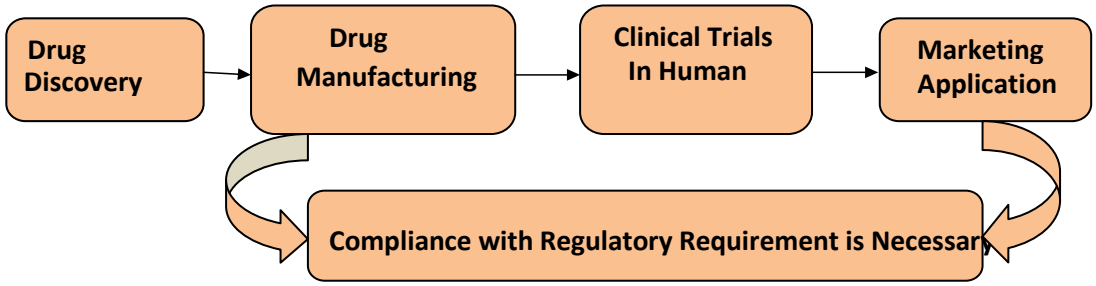

Figure 1. Regulation of Drug Approval Process (1-2)

The phases of product life cycle are:

- Business Development
- New product development
- Manufacturing
- Common technical document compilation
- Submission in the regulatory affairs
- Approvals/ Marketing Authorization
- Post approval Compliance
- Variations
- Renewals (After expiry of approved license)

2. Phase-1: Business development

A business development plan in transferring should define the company's commitment to international trade, export pricing strategy, reason for exporting, potential support markets and customers, export financing alternatives, legal requirements, methods of foreign trade, transportation method, overseas partnership, and investment capabilities. The main purpose of the international business development plan is to ready your business to enter the international market. The general working principles guides to creating the international business development plan as below;

I. Product or services: Choosing the right product and to recognize products with export potential needs careful considerations on products that are profitable distributed in the markets.

II. Planning: The planning phase allows looking at future business operation and foreseeing possible things to be happened.

III. Goal set: Goal set to plan the entry into the global market and shape the business goals can be challenging. The company must have short term and long-term goals for the business.

IV. Market analysis: Knowing the future trends, talking the people within the same business, researching, and attending trade affairs, data analysis and seminars will be helpful in the industry analysis.

V. Market and pricing strategy: The marketing strategy is very important in sales, as it will involve what the market requires and how much risk a company is willing to take. Pricing strategy also considers value added services in bringing the product to the international market.

3. Phase-2: New product development

The main coordinating function works exclusively under new product development are following:

- Formulation and development for formulation development feasibility
- Analytical development laboratory for manufacturing and product design feasibility
- International regulatory affairs for checking regulatory requirements of a product
- International business development team

The various operational tools generally used by product development team in the process of new generic product development are given below:

New Product Requisition Form (NPRF) verification and detailing

This form is to be used for placing requisition for development of new product or for registration of an existing product with the company. This form is basically consisting of following things:

Master List

- Product name
- Dosage form
- Route of administration
- Strength
- Container closure system
- Packaging material
- Total market size quantity wise
- Expected sales quantity, sales price and price trend over
- Market growth rate per year
- Details of reference product and reference company
- Competitor's details in terms of strength, volume, container, quantity in sales, price, etc.
- Registration details and available regulatory guidelines

Techno Commercial Feasibility (TCF): This is also called as product design document, this document or data is generally used to ensure the technical feasibility for procuring the raw material, and other materials or machinery used for new product development and for commercial manufacturing of finished product and testing. It basically contains the following information:

- General information (product name, strength)
- Product formulation development and manufacturing feasibility analysis with technical support of formulation and analytical development team
- Costing details of the product per unit costing and overall costing in development
- Container closure and packing material information
- Labelling information for both primary and secondary packing
- Storage conditions
- Formulation specification including excipients and product formulation
- Market sample of innovator
- Manufacturing process and manufacturing facilities for product scale up
- Type of sterilization and type of tentative timeline
- Product feasibility data

The development procedure for the new product is mainly involves of following steps:

I. Pre-formulation plan:

After formal approval of product for product development, the product development team will start literature survey and following points should be ensured,

- Innovator product study
- Physicochemical parameters
- Formulation and composition
- Stress condition study (Heat, Oxygen and light sensitivity)
- Container closure system
- Stability study
- Compatibility study
- Storage condition

Based on available data, summary report should be prepared and prepare for next step.

II. Final formulation and testing of batches:

- Final formulation study plan will be presented with rationale, data analysis of Pre-formulation study and plan for first final formulation study
- One batch would be taken for laboratory stability chamber as per ICH guidelines on different temperatures and humidity
- Perform the stability study on the finalized analytical method at different intervals as per ICH for critical parameters like pH, related substances, assay of antioxidant, preservative and assay of active drug substances
- After analysing the one-month results of first batch, the next two batches with the final formulation will be taken
- If any adverse analytical observation is made in the first batch results, the further two batches will not take out but reformulation or investigation will be made
- Two batches of final formulation will be taken and the batch size of the batches will be 1/5-1/10 of exhibit batch size
- These three batches stability study will be continued for six months
- After checking the stability data of stability batches for 3 to 6 months, the next steps for further development will be taken.

III. Records:

The record section contains the following documents;

- Product development report
- Literature survey report
- Innovator sample testing report

- Drug-excipient compatibility report
- Lab trial batch record
- Draft master batch document
- Stability data
- Diluent compatibility report
- Essential similarity report with innovator sample
- Extractable leachable study report
- Supplier certificate of analysis of raw material, excipients, containers, closure

4. Phase-3: Manufacturing

There are two types of manufacturing process of pharmaceutical products, sterile and non-sterile products. The manufacture of sterile products is subject to special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality assurance is particularly important, and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.

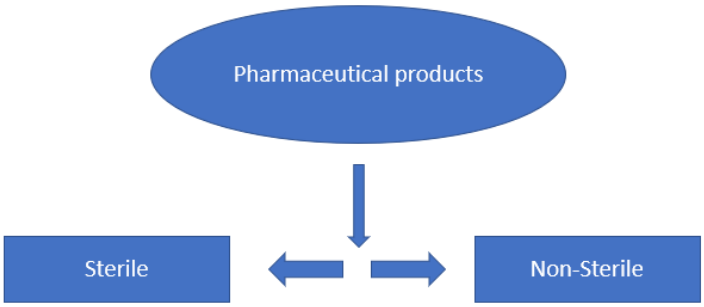

Figure 2. Pharmaceutical Products (1-2)

Marketing authorization

A medicinal product may only be placed on the market in the European Union when a marketing authorization has been issued by the competent authority of a Member State for its own territory or when an authorization has been granted in accordance with regulation (EEC) No.2309/93 for the entire community. The marketing authorization holder, which encompasses the terms 'holder of the marketing authorization' and 'person responsible for placing the medicinal product on the market', must be established within the EEA. The MA can be given to the applicant by the following procedures: (3-8)

- National procedures
- Decentralized procedures
- Mutual recognition procedure
- Centralized procedure

CTD means common technical document, is an internationally agreed upon format for the preparation of well-structured applications to be submitted to regulatory authorities in the three ICH regions- Europe, US and Japan. The main objective is the preparation and verification of the full Module1-5 of dossier in CTD format for submission in Europe and ORM. This is valid for all types of applications-National, centralized, MRP (Mutual recognition procedure) and DCP (Decentralized procedure).

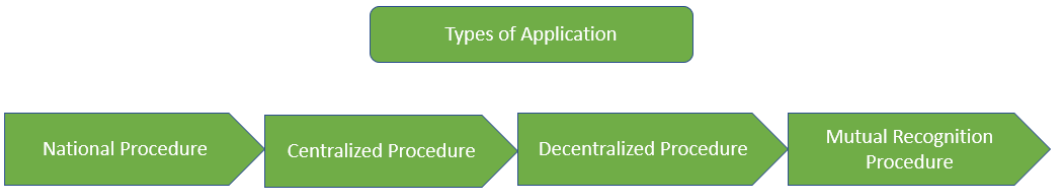

Figure 3. Types of applications for submission in Europe (1-2)

Mutual recognition procedure:

With the Mutual Recognition Procedure, a product is first authorized by one country in the Europe in accordance with the National Procedures of that country. Later, further Marketing Authorizations can be hunted from other European countries, who rather than conducting their own review, agree to identify the decision of the first country.

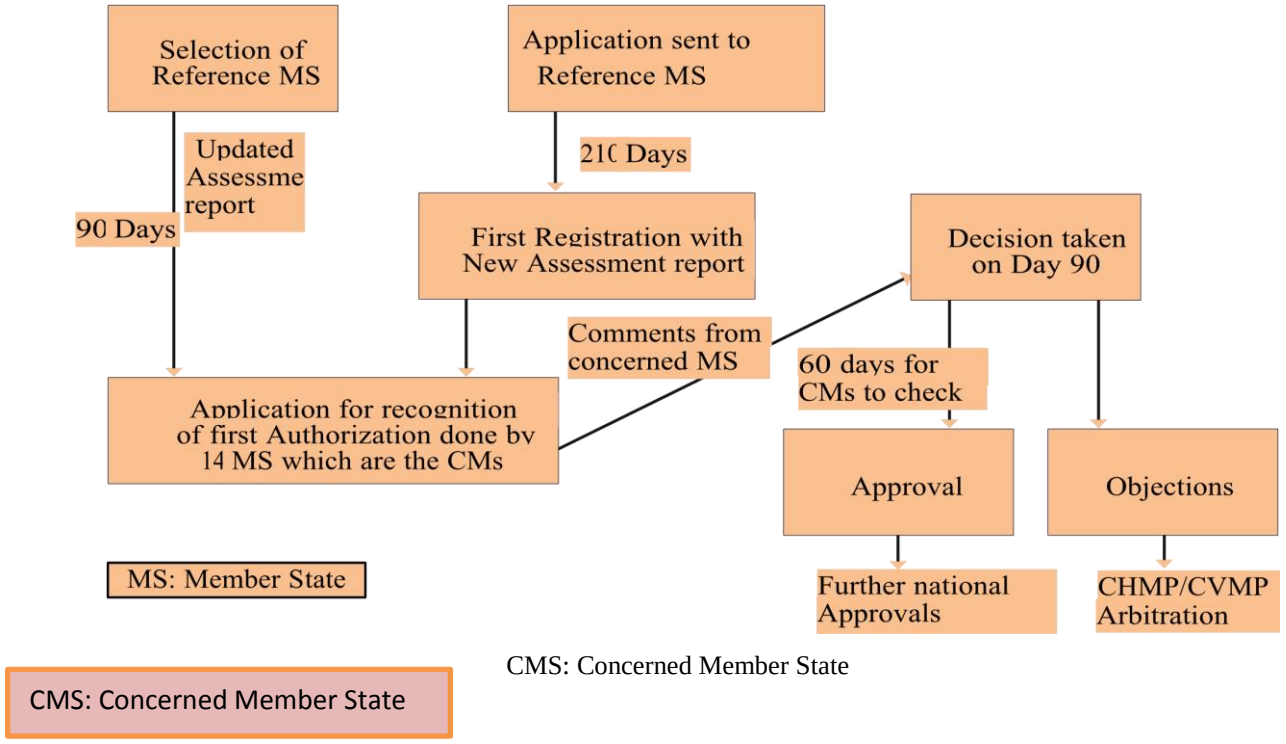

Figure 4. Mutual Recognition Procedure for Drug Approval Process in EU (1-2)

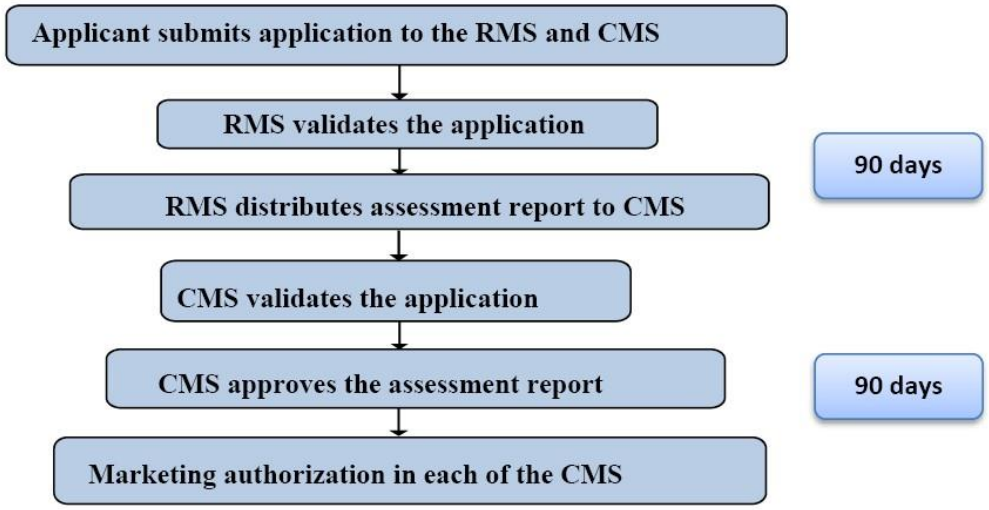

Figure 5. Mutual Recognition Procedure for Drug Approval Process in EU (1-2)

Centralized procedure:

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

Decentralized Procedure:

To receive marketing authorizations in numerous member states, the centralized procedure is not mandatory; in such case the decentralized procedure is to be used. An application is submitted to competent authorities of each of the member states, where a marketing authorization is to be required. The information like quality, efficacy, safety, administrative information shall be submitted and a list of all Concerned Member States (CMSs) and one-member state to act as Reference Member State (RMS). A draft assessment report on the medicinal product is prepared and the CMS and the RMS confirm the application within a time frame of 14 days. The RMS prepare draft summary of product characteristics, labelling and package leaflet within 120 days. This report can be approved within 90 days.

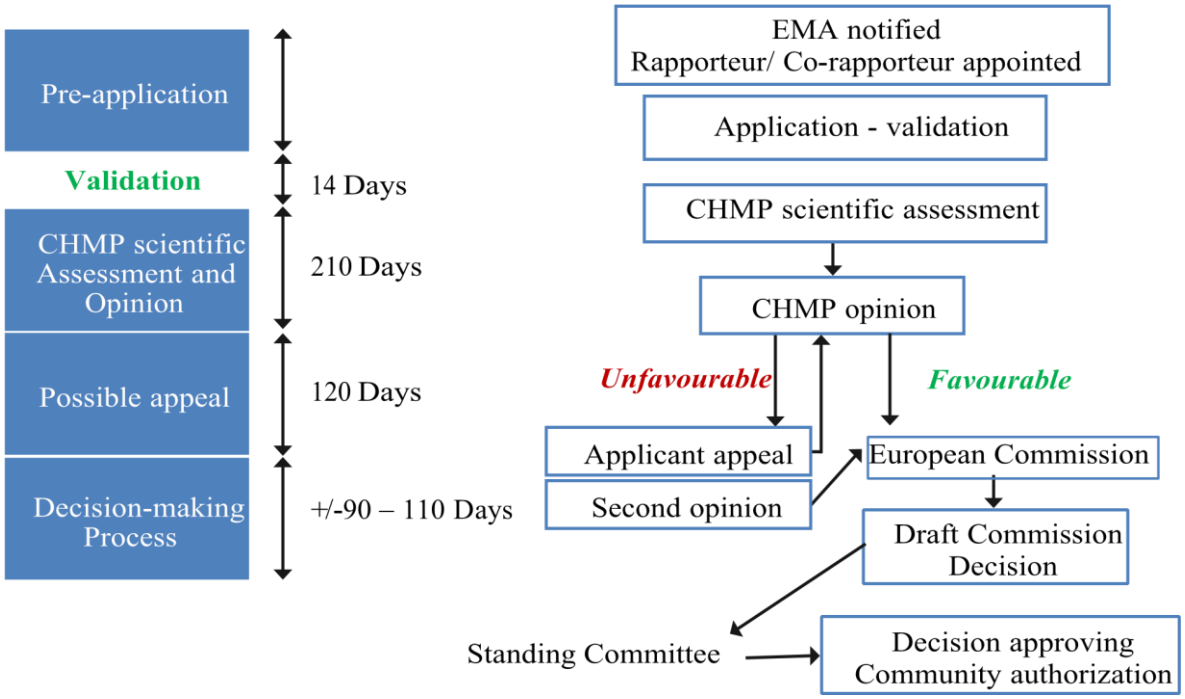

Figure 6. Centralized Procedure for Marketing Authorization in EU (1-2)

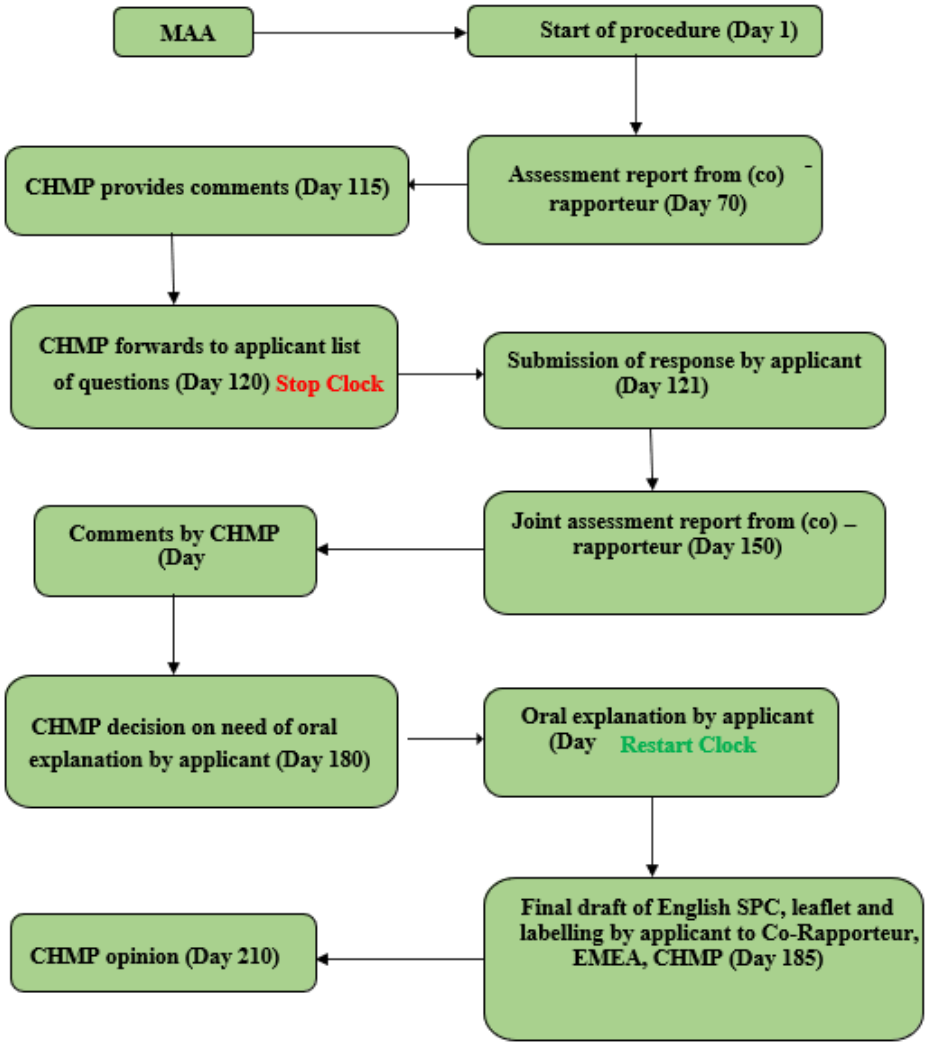

Figure 7. Centralized Procedure for Marketing Authorization in EU (1-2)

However, if a medicinal product is supposed to cause potential serious risk to public health, CMS will inform to other CMS, RMS and applicant and further conclusion in this regard is taken within 30 days. Within 60 days of the announcement of the points of disagreement, all member states reach to an agreement on the action to be taken.

After a conclusion to an agreement of the member states, the RMS records the agreement and informs to the applicant. However, if the member states could not reach an agreement, then CHMP intervenes and take a final decision keeping in view of the written or oral explanations of the applicant.

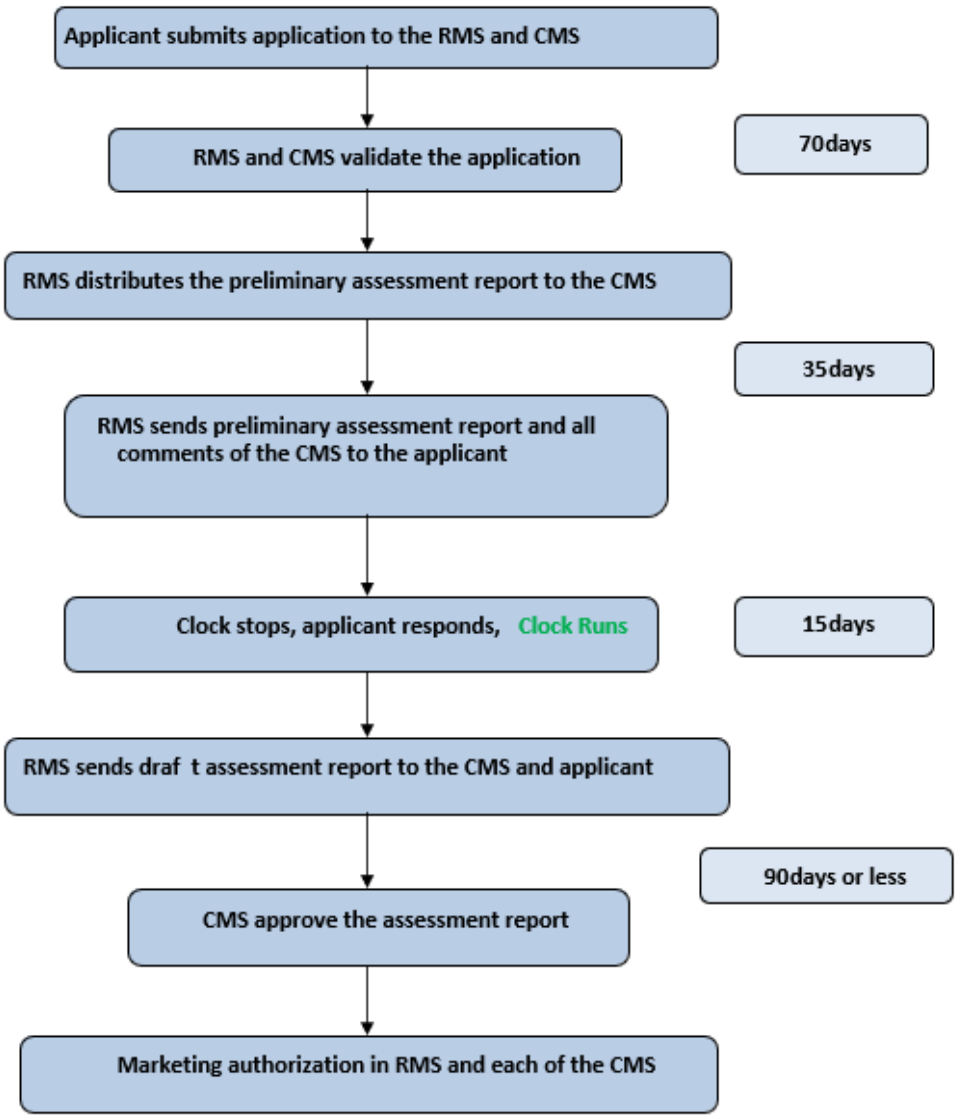

Figure 8. Decentralized Procedure for Marketing Authorization in EU (1-2)

5. Common technical document compilation

CTD having 5 different sections or modules as follows:

a) Administrative information (Module 1):
b) Quality overall summary-QoS (Module 2):
c) Quality (Module 3):
Drug Substance (DS):

Drug Product (DP):

Appendices:
Regional information:
Literature references:

d) Non-clinical reports (Module 4):
Module 4 is a non-clinical study of molecule and its formulation. This can be the country specific requirement. It contains pharmacokinetics and pharmacodynamics study in animal, toxicity studies. (9,10)

e) Clinical reports (Module 5):
Module 5 is a clinical study of molecule and its formulation. It contains pharmacokinetics and pharmacodynamics study in humans, safety and efficacy study in humans. For all the countries Module 5 is not required. This can be the country specific requirements.

6. Submission in the regulatory authority (Phase-5)

Before submission all 5 dossier modules shall be prepared to meet the submission plans. The main objective for submission in the regulatory authorities is

to get the approval and grant of marketing authorization to market the approved product.

7. Market Authorization Approval (Phase 6)

The purpose to approve the products and allow them to launch into the registered markets. (11-17)

8. Post approval compliance (Phase 7)

This phase arises after formal MA approval and/or during the commercial production and supply of goods to approved market. This phase endorses the internal process to handle and respond to these changes. The main content that come under this phase of life cycle are;

- ❖ General Compliance Query from Customer
- ❖ Technical or GMP Agreements
- ❖ Batch release documents
- ❖ Technical package for commercial productions

9. Variations (Phase 8)

In accordance with the Directives 2001/83/EC for medicinal products for human use, and Council registration (EEC) 2309/93 a marketing authorization is granted for a period of 5 years, renewable upon application 3 months before expiry. Throughout the life of a medicinal product, the marketing authorization holder is responsible for the product which circulates in the market place and is also required to take into account technical and scientific progress, MA holders may, in addition, wish to alter/improve the medicinal product or to introduce an additional safeguard during the period of five years.

Variation types:

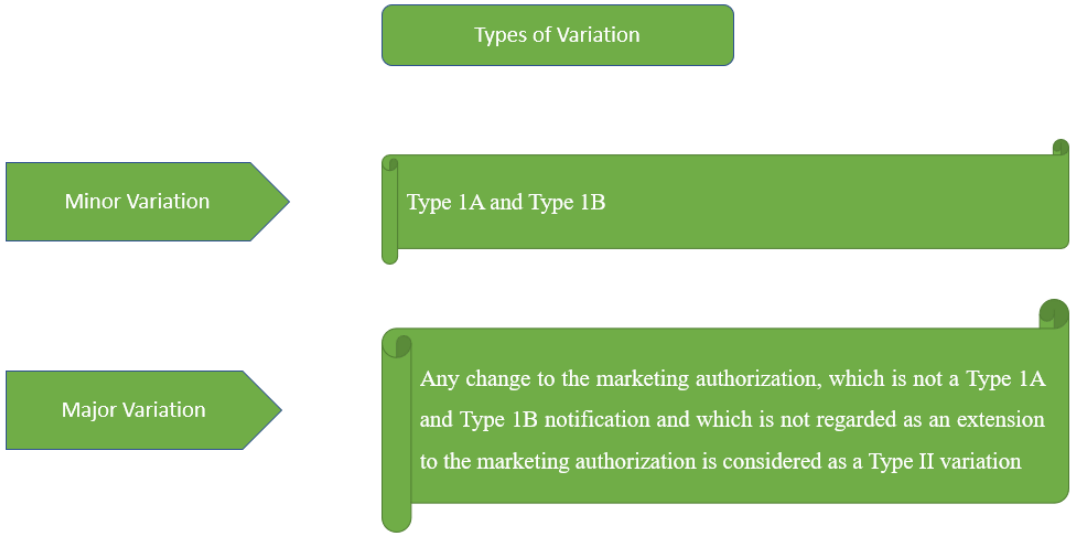

Figure 9. Types of Variation filing (1-2)

10. Renewals, after expiry of license (Phase 9)

In accordance with directives 2001/83/EC for medicinal products for human use, and council regulation (EEC) 2309/93 a marketing authorization is granted for a period of 5 years, and if applicant wants to renew the license, then it is mandatory to apply the renewable application 3 months before expiry.

11. Results and Discussion

Through studying the overall stages of generic product life cycle exclusively for the regulated Europe market, the following results are concluded:

- ❖ The average time span of a generic product (sterile/aseptic) life cycle start from its identification to till expiry of marketing authorization license is near about 30 months and exclusive 5 years of marketing license. The most crucial phase in whole life cycle is submission in the regulatory agencies and their on-time approvals.
- ❖ For generic drugs Module 3 (Quality part) is of most important. In quality part section 3.2.S for drug substance manufacturing, characterization, control of drug substance and stability section are the critical. In section 3.2.P for drug product, pharmaceutical development, manufacturing and control of drug product are most crucial.
- ❖ This is the most critical part of entire product life cycle, due to very minor mistakes during the submissions, several applications at the end stages have been cancelled with loss of huge amount of expenses spent on product development, manufacturing, registrations, etc. Except national registration which is valid for only one country inside Europe, remaining procedures like decentralize procedure and mutual recognition procedure are strict time bound procedures and should be completed under framed timelines given by authority, otherwise application will be send to community referrals for further decisions.
- ❖ Marketing authorizations approval for a drug is specified part of Europe for a defined time period. The approval letter should be methodically checked after receiving directly from the health authority like approved brand name of drug product, approved market pack size as well as fill volume. In addition

to this please verify the correctness of unique MA number granted to particular product.

- This phase is directly linked with previous phase of post approval compliance because it may be the previous one who decides whether MA holder needs to file a variation application or not. The critical period under variations is that when applicant applies for any particular variation application, compilation of required documents because variation applications are generally rejected even if a single document is missing or if there is a minor mistake and the worst part is that the fees for variation applications is non-refundable in any case.
- In this phase, If MA holder wants to market the same product, then MA holder needs to reapply the application before 3 months from the date of expiry of existing license. Common technical document, CTD is an internationally agreed upon format for the preparation of a well-structured presentation for applications to be submitted to regulatory authorities in the three ICH regions of Europe, USA and Japan. It is proposed to save time and resources and to facilitate regulatory review and communication. The CTD gives no information about the content of a dossier and does not indicate which studies and data are required for a successful approval. Regional requirements may affect the content of the dossier submitted in each region. Therefore, the dossier will not necessarily be identical for all regions. The CTD indicates an appropriate format for the data that have been acquired. (18,19)

12. Conclusion

The phases of mentioned product cycle management are designed conferring to the regulatory framework and after study it has been concluded that, the drug regulations should be proficiently comprehensive and flexible to encounter the purposes of drug regulation.

In general, the drug regulation must be as below,

- The roles, responsibilities, right and functions of all parties involved with drug regulation, including those of the regulators and regulates.
- Create the administrative bodies necessary for implementation of drug regulations and define their structural and functional affiliation.
- Create mechanisms to ensure that all responsible parties are licensed and inspected to ensure compliance with the provisions of drug legislation as well as with the standards and specifications set for persons, premises, and practices.
- Define the norms, standards, and specifications necessary for ensuring safety, efficacy and quality of the drug products as well as the appropriateness and accuracy of drug information.
- States the terms and conditions under which licenses to import, manufacturer, distribute, sell, supply, and promote drugs will be suspended.
- Establish the administrative measures and legal sanctions that will apply when provisions of drug legislations are violated.

The pharmaceutical industry is now perhaps the most highly regulated of all industries demanding a high level of information to be submitted to regional health authority bodies before a pharmaceutical product is brought to the market. Regulatory authorities are the functional responsible for obtaining and maintaining licenses to market medicinal products in as many countries as is necessary. According to the present laws all organizations involved in the development and marketing of medicinal products are legally required regulatory support. This could be provided internally or via an external service provider such as a regulatory consultancy that provide regulatory services.

Pharmaceutical company should keep a close eye on the changing regulation and should consult with regulatory consultant for proper filing, so that they can enter without any hurdles.

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Conflict of interest

The authors declare that there are no conflicts of interest.

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