

Product Life Cycle Management in Regulated Market of Europe

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Received date: Jan 20, 2017; Accepted date: Jan 21, 2017; Publish date: Jan 28, 2017

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Abstract

To study the product life cycle management in the regulated market of Europe Under this title the scope of work is defined as: To study the practical aspects of different phases of life cycle of generic sterilized injectable product in regulated market of Europe, to study the European standards and requirements for registration of injectable drugs, to study the lifecycle 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, live case studies and live operational projects at International Regulatory affairs department at Claris life sciences Ltd to study, prepare, compile and submit the data according to the CTD format in the regulatory agencies of Europe as critical phase of life cycle. The pharmaceutical industry is now perhaps 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 market place. Each country holds different regulatory department. In this scenario, the product life cycle management in regulated market of Europe upholds a significant value.

Keywords: CTD; EMEA Guidelines; MA; Regulatory affairs

Introduction

International Regulatory Affairs does not have a single definition and it's frequently defined in number of ways. One definition is the "act of gathering and analysing regulatory information and monitoring the current regulatory climate" [1]. However it is more than just gathering information as this is then used to generate regulatory strategies and gain a competitive advantage for obtaining regulatory approvals. It is also described as understanding the Pharmaceutical laws, rules, regulations knowing how the regulations are applied and practiced and applying the regulatory knowledge to specific situations.

Regulatory affairs also sometime called as Government affairs, is a professional with in regulated industries such as pharmaceuticals. The pharmaceutical biotechnology and 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 in pharmaceutical industry aim in the protection of human health. Regulation promotes various activities so as to ensure safety, efficacy and quality of drugs. The regulations are applied to all drugs from new, innovative to long established products. It also applies to drugs from different sources, regardless of whether they are produced domestically or imported by the public or private sector.

Since a long time World Health Organization (WHO), international organizations and many countries are trying to strengthen the regulatory process at national and international level. There is no drug available without terms the terms of medical researchers and other

specialists who work to make sure it received Food and Drug Administration approval. Some of the important organizations working as drug regulatory authorities' worldwide are given below:

- Therapeutic Goods Authority (TGA) - Australia [2]
- Therapeutic Product Directorate (TPD) - Canada [3]
- European Medicine Agency (EMA) - Europe [4-26]
- Agencia Nacional Vigilancia Sanitaria (ANVISA) - Brazil [5]
- Medicines and Healthcare products of Regulatory Agency - UK [27]
- Ministry of Health and Labour Welfare (MHLW) - Japan
- Food and Drug Administration (FDA) - USA
- Medicine Council Control (MCC) - South Africa
- Health Science Authority (HAS) - Singapore
- Drug Controller General of India (DCGI) - India [28]

The EMEA is a decentralized body of the European Union with headquarters in London. Its main responsibility is 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 [29].

Materials and Methods

The materials used for the study are EMEA Guidelines and directives, EUDRA Guidelines, Regulatory communications and conferences with the regulatory expertise personals, Regulatory journals and regulatory updates, Internet, Standard operating procedures and different case studies of International Regulatory affairs department at Claris life sciences Ltd, Ahmedabad.

The method used for the study of product life cycle management in regulatory markets of Europe is described by different phases. The phases of product life cycle are:

- International business development;
- New product development;
- Manufacturing / Production;
- Common technical document compilation;
- Submission in the regulatory affairs;
- Approvals/ MA;
- Post approval Compliance;
- Variations (if any);
- Renewals (After expiry of license).

International business development (Phase-1)

An international business development plan in exporting 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 place. The general working principles guides to creating the international business development plan:

Product or services: Choosing the right product to offer internationally is very important; to recognize products with export potential needs careful considerations on products that are profitable distributed in the domestic market.

Planning: The planning stage enables you to look at future business operation and foresee possible things to happen.

Goal setting: This step is very important in planning your entry into the global market, and shaping the business goals can be quite exciting and challenging. The company must have short term and long term goals for your business.

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

Market factor assessment: Analysing and assessing certain factors of market is another important step. Market factors include demographic/physical environment, political environment, economic environment, market access, product potential and local distribution and production.

Market and pricing strategy: The chosen marketing strategy is very important in international sales, as it will involves 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.

New product development (Phase-2)

The main coordinating function works exclusively under new product development are following [30]:

- 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 first two functions are considered as the back bone for new product development. The various operational tools generally used by NPD team in the process of new generic product development are given below:

NPRF (New Product Requisition Form) 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 consists of following things:

- Product name,
- Dosage form,
- Route of administration,
- Strength, volume, pharmaceutical form of different variants,
- Container closure system,
- Secondary packaging material,
- Total market size quantity wise,
- Expected sales quantity, sales price and price trend over last 2-3 years,
- 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 guidelines.

After the NPRF detailing, the department will update the product list and will send the priority wise product list (as in accordance with business development team) along with the market samples to the following functions. Product list will contain molecule, strength, and volume and container detail along with name of country/region.

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 of product (product name, pack size, strength);
- Product formulation development and manufacturing feasibility analysis with technical support of formulation development team and analytical development lab;
- Costing details of the product per unit costing and overall costing in development;
- Container closure/packing material information;
- Labelling information for both primary and secondary packing;
- Storage conditions;

- Formulation specification including excipients and product formulation;
- Resource assessment data;
- Market sample of innovator;
- Manufacturing process and manufacturing facilities for product scale up;
- Type of sterilization and type of tentative timeline;
- Product feasibility data;
- Analysis report of commercial feasibility together with costing department based on the costing data and market potential data received from International business development team.

Product development: Under this section formulation development and analytical development team will act co-ordinately with NPD team. The major coordinating activities done by NPD team with other departments are as follows:

- After finalization of the product, the NPD team will send the details of that particular product to the below mentioned departments;
- API-Sourcing for procuring samples for development;
- Formulation development and analytical development lab-for development plan;
- International regulatory affairs-For artworks, brand name and label designs.

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

a) Preliminary formulation plan: After formal approval of product for product development, the product development team will start literature survey. In literature survey, following points should be ensured:

- Innovator product study;
- Physicochemical parameters;
- Formulation and composition;
- Heat, oxygen and light sensitivity;
- Container closure system;
- Stability and compatibility information;
- Storage condition.

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

b) Preformulation: The Preformulation study plan will include the following:

- Proposed formulation;
- Rationale of formulation;
- The number of studied to be undertaken and challenge studies to be made;
- The batch results of such Preformulation study will be summarized and analysed and presented in the required format.

c) Final formulation evaluation and testing

- After Preformulation study, final formulation study plan will be presented with rationale, data analysis of Preformulation study and plan for first final formulation study;
- One such batch would be taken for laboratory stability 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.

d) 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.

Stability batch: The next step after TTD transfer to the manufacturing team, the NPD will proceed towards the stability batch at manufacturing site. The roles and responsibilities of NPD team for successful take off of stability batch are describing below:

- NPD team will communicate to API-sourcing, the stability batch date so as to ensure procurement of material in time;
- NPD team will communicate to quality control, IPQA, quality assurance micro, corporate quality assurance when material is to be received in store;
- NPD team will ensure that TTD reaches to plant at least 15 days or on specified time before material;
- NPD team will ensure that plant IRA prepare specifications (raw materials, packing material, in-process product testing, finished product) and method of analysis within 15 days or on specified time of technology transfer document received;
- NPD team will provide packing details of API/Excipients to plant IRA and QC;
- NPD team will coordinate with API sourcing for ensuring COA of API reach to plant along with material;
- NPD team will inform to production planning, quality control, In-process quality assurance, quality assurance, validation, stability and IRA before 10 days or as per of production date;
- NPD team will ensure IPQA provides MBD within 5 days of receipt of TTD, provided all details available;
- NPD team will ensure TTD goes to plant IRA and reviewed by QC, QA and production manager;

- NPD team will ensure F and D manger reviews MBD within 3 days;
- NPD team will ensure final MBD reviewed by IRA;
- NPD team will ensure process order by IPQA on the day of process order released;
- Team Lead will get monthly updates on the stability of the product;
- If, batch is successful, team lead will start overseeing registration process.

Manufacturing/Production (Phase-3)

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.

General aspects:

1. The manufacture of the sterile products should be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency;
2. The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area. Manufacturing operations are divided in two categories; firstly those where the product is terminally sterilized and secondly those which are conducted aseptically at some or all stages;
3. Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. In order to meet "in operation" conditions these areas should be designed to reach certain specified air-cleanliness levels in the "at-rest" occupancy state. The "at-rest" state is the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present. The "in-operation" state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.

For the manufacture of sterile medicinal products 4 grades can be distinguished.

Grade A: The local zone for high risk operations, e.g.: filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station.

Grade B: For aseptic preparation and filling, this is the background environment for the grade A zone.

Grades C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

Common technical document compilation (Phase-4)

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) [31]. CTD having 5 different sections or modules as follows:

Regional administrative information (Module 1): This notice to applicants has been prepared by the European Commission, in consultation with the competent authorities of the Member states and European Medicines Agency. Module 1 includes the following sections:

- Cover letter;
- Application/MAA form; Latest version of the application form should be used by referring notice to applicant, Volume 2 B;
- Product information;
- Information about the Experts;
- Specific requirements for different types of applications;
- Non-GMO, especially for biotech products;
- Information relating to Orphan market exclusivity;
- Information relating to pharmacovigilance;
- Information relating to clinical trials.

Quality overall summary-QoS (Module 2): Module 2 is the summary of Module 3, 4 and 5 and is known as quality overall summary (QoS). This section should contain the brief information about the product. It should be not more than of one page.

Quality (Module 3): Module 3 is a quality part. Module 3 is having major two sections, Drug Substance (DS) and Drug Product.

For preparation of both the sections refer to guideline from CPMP and ICH. For DS section we have to provide open part of EDMF from API manufacturer.

Non clinical reports (Module 4): Module 4 is a non-clinical study of molecule and its formulation. For all the countries Module 4 is not required. This can be the country specific requirement. It contains pharmacokinetics and pharmacodynamics study in animal, toxicity studies. For above mention studies we have to collect the abstracts and references from internet (responsibility of clinical trial team).

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 above mentioned studies we have to collect the abstracts and references from internet (responsibility of Clinical trial). For all the countries Module 5 is not required. This can be the country specific requirements [32].

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.

Types of Submission:

Decentralized Procedure (DCP), for Europe only: The decentralized procedure should be used for products that have not yet received authorization in an EU country. The applicant may request one or more concerned Member states to approve a draft assessment report,

summary of product characteristics, labelling and package leaflet as proposed by the chosen reference Member state in 210 days. The two groups, CMD (h) and CMD (v) also work for the facilitation of the decentralized procedures. DCP is a time bound procedure and applicable to all the CTD submission applications through decentralized procedure for all the generic products for entire European countries. The DCP is a single procedure that could end at different stages taking into account:

- Harmonization of originators SPCs;
- The quality;
- The assessment report.

It is possible to end the procedure at Day 105, if consensus is reached, at Day 120, at Day 150 and at Day 210 (followed in each case by 30 days for the national step-text translation/granting of marketing authorization). Also at Day 270, if the coordination group (CMD) achieves agreement.

Mutual Recognition Procedure (MRP) for Europe only: Mutual recognition means that EU countries may approve the decision made about a medicinal product by another EU country. The pharmaceutical company submits their application to the country chosen to carry out the assessment work, which then approves or rejects the application. The other countries have to decide within 90 days whether they approve or reject the decision made by the original country. Two groups are working for the facilitation of the MRP:

1. For human medicinal products, the CMD (h)-Coordination group for mutual recognition and decentralized procedures (human);
2. For veterinary medicinal products, the CMD (v)-Coordination group for mutual recognition and decentralized procedures (veterinary).

If the member state (s) fails to reach an agreement during the 60-day procedure of the pre-referral, a referral to the CHMP/CVMP for arbitration may be made through its secretariat at the EMEA [33].

National registration process (country specific): The national procedure is country specific in nature and depends on country specific registration process, here in national procedure submission there is no defined or standard timelines for the duration of procedure as in compare to the MRP or DCP.

Generalized procedural steps:

- Stability batch manufacturing as per NPD plans;
- Documents from FRD, ADL, QA, QC, API and production department;
- Prepare the Master dossier;
- CTD for submission in accordance with BD plans;
- CTD/CD/Paper files ready;
- Submission to the agency;
- Validation or screening of application;
- Dossier review queries;
- Query response;
- MS grant/License Approved;
- Technical agreements, Art works and technical package for commercial production and supply;
- Variation (if any) and compliance requests (if any).

MA grant/Approval (Phase-6)

The primary purpose of any rules governing medicinal products is to safeguard public health. However, this objective must be achieved by means, which do not hinder the development of the pharmaceutical industry or trade in medicinal products within the community. Thus the pharmaceutical legislation of the European community has consistently pursued the twin objective: the protection of public health and the free movement of medicinal products.

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 (national authorization) 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:

- Independent National procedures;
- DCP-Decentralized procedures;
- MRP-Mutual recognition procedure;
- Centralized procedure.

Post approval compliance (Phase-7)

This phase is come in to action after formal MA approval and/or during the commercial production and supply of goods to approved market. As International Regulatory Affairs is the single window for information receipt from all business partners, regulatory authorities, there are many types of compliance or regulatory supplementary information request received. This phase recommends the internal mechanism to handle and best respond to these.

The main content that is wisely 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.

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 three 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:

Minor variation: Type 1A and Type 1B are considered to be minor variations.

Major variation: Any change to the marketing authorization, which is not a Type 1 A and Type 1B notification and which is not regarded as an extension to the marketing authorization is considered as a Type II variation.

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 the renewable of license, then it is mandatory to apply the application three months before expiry.

General aspects:

There are broadly two options for applicant after the expiry of license:

1. Withdrawal of product from the market due to the reasons like saturation of the market for that particular product, low sales or less profit, narrow margins, etc.
2. Apply for the Extension for the license application.

Results and Discussion

By studying the overall phases 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 month plus exclusive 5 years of marketing license.

The most critical phase in whole life cycle is submission in the regulatory agencies and on time approvals.

All phases are inter-related with each other and highly depend on other like there should be high understanding and coordination between formulation development, analytical development and new product development team. These three are regarded as base pillars for very first launching of product in any market.

Every phase has some critical parameters, these are described below:

- International business development: Product identification, and searching of trustable business partners who are having product release license as well as approved testing site in Europe in order to release; test; distribute and market the approved product in Europe.
- New product development: technical and commercial feasibility, final formulation study and stability batch release approval.
- Manufacturing/Production: In the manufacturing process of aqueous injections and fat emulsion for injection, the critical steps are Mixing, Filling and Sterilization. In addition to these the other areas of criticality are different validation studies and microbiological testing's on ongoing batches.
- Common Technical department compilation: For generic drugs Module 3 (quality part) is of utmost important. In quality part section 3.2 S for drug substance manufacturing, characterization, control of drug substance and stability section are critical one. In section 3.2 P for drug product, pharmaceutical development, manufacturing and control of drug product are most critical one.
- Submission in the regulatory authorities: This is the most critical part of whole product life cycle, due to very small mistakes or carelessness during the submissions, various applications at the end stages have been cancelled with loss of huge amount of expenses spent on product development, manufacturing, registrations, etc.

As mentioned earlier, 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 complete under fixed timelines given by authority , otherwise application will be send to community referrals for further decisions.

- MA Grant / approval: Marketing authorizations grant or approval for market a drug is specified part of Europe for a defined time period. In this the grant or approval letter should be checked after receiving directly from the concerning authority like approved brand name of drug product, its concentration, approved market pack size as well as fill volume. In addition to this please verify the correctness of a unique MA number granted to particular product after approval, content of summary of product characteristics.
- Post approval compliances: This simply means to ensure that whatever the final information that has been submitted to the regulatory body in getting the product registered is followed or not during commercial production and marketing of product in the Europe.
- Variations: 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.
- Renewals: As such this phase does not have any specific requirements in terms of criticality as comparison with the other phases of life cycle. If MA holder wants to market the same product then MA holder needs to reapply the application before three months from the date of expiry of existing license.

Common technical document: The 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 intended 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.

Conclusion

The phases of above mentioned product cycle management are designed according to the regulatory framework and after study it has been concluded that, the drug regulations should be efficiently comprehensive and flexible to meet the objectives of drug regulation.

In general, the drug regulation must:

- State 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 relationship.

- 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 governments before a pharmaceutical product is brought to the market place. Regulatory authorities can be said to be the function 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 to have some form of regulatory support. This could be provided internally or via an external service provider such as a regulatory consultancy that provide regulatory services.

Acknowledgements

The authors are thankful to Claris life Sciences Ltd, to carry out the work with world class facilitated International Regulatory Affairs department.

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