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TECHNICAL STEPS AND CHALLENGING DECISIONS DURING REGISTRATION OF DRUG PRODUCTS

K. Prasanna Teja, D. Nagarjuna Reddy*, M. V. Nagabhushanam, Konda Ravi Kumar and Munagala Gayatri Ramya

Hindu College of Pharmacy, Amaravathi Road, Guntur. A.P, India.

***Corresponding Author: D. Nagarjuna Reddy**
Hindu College of Pharmacy, Amaravathi Road, Guntur. A.P, India.

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INTRODUCTION

Regulatory Affairs in the Parma Industry may be defined as "The interface between the pharmaceutical company and the regulatory agencies across the world." Regulatory affairs is a comparatively new profession which developed from the desire of governments to protect public health by controlling the safety and efficacy of products[1-6] in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines. Regulatory agency in the present context may be defined as "The competent government agency which is responsible for ensuring that medicines work and are acceptably safe."

Goals of Regulatory Affairs as profession

- Protection of human health.
- Ensuring safety, efficacy and quality of drugs.
- Ensuring appropriateness and accuracy of product information.

Roles of Regulatory Affairs professionals

- Act as a liaison with regulatory agencies
- Preparation of organized and scientifically valid NDA, ANDA, INDA, MAA, DMF submissions.
- Ensure adherence and compliance with all the applicable cGMP, ICH, GCP, GLP guidelines, regulations and laws.
- Providing expertise and regulatory intelligence in translating regulatory requirements into practical workable plans.
- Advising the companies on regulatory aspects and climate that would affect their proposed activities.

Apart from the above main roles, there are various other roles which Regulatory Affairs professionals play.

General work profile of a Regulatory Affairs professional in an API (Active Pharmaceutical Ingredient) manufacturing company

- Filing a DMF/ASMF with regulatory agencies in support of the NDA/ANDA/INDA/MAA filed by a Formulator (Drug Product manufacturer who uses API of that particular API manufacturing company).
- Filing dossier of API with EDQM for obtaining CEP.
- Assessing and filing amendments/variations to the information (which may be related to manufacture, control, stability studies etc) in DMF/ASMF/Dossier of particular API with the Regulatory agencies. Major amendments are to be reported prior to their implementation while minor amendments may be reported annually. The classification of amendments will be dealt in the later posts.
- Taking approval of customers of API before implementing any major changes regarding the information mentioned in DMF/ASMF/Dossier. The updated DMF/ASMF may be submitted to the customer simultaneously along with amendments/variations filed with the agency.
- Preparing and submitting Open part/Applicant's part of DMF to the customers of API (Drug products manufacturer) which may be filed by customer with the Regulatory agency.
- Preparing and submitting the LoA (Letter of Access/Letter of Authorization) to the API[7-11] customers and Regulatory Agencies. LoA is the letter which authorizes the regulatory agency to review the DMF /ASMF of the API manufacturer against the NDA/ANDA/MAA of the API customers (Formulators).
- Preparing Technical Packages for existing/ prospective customer for initial assessment of the API.
- Filing Annual/Biannual/Quinquennial reports (Which contain list of changes to the DMF/ASMF/Dossier) with the regulatory agencies.
- Maintenance of the complete history of each API (Filing history with agencies/customers, amendments, annual reports).

- Taking part in the drug development process by advising the R & D scientists regarding various guidelines, laws and regulations.

General work profile of a Regulatory Affairs professional in a Drug Product /Finished Product/Formulation manufacturing company

- Filing a NDA/ANDA/MAA of drug products with regulatory agencies for getting marketing approval.
- Assessing and filing supplements/amendments/ variations to the information (which may be related to manufacture, control, stability studies etc.) in NDA/ANDA/MAA with the Regulatory agencies for prior approval or after their implementation. Major supplements/amendments are to be reported prior to their implementation while minor supplements/amendments may be reported annually. The classification of amendments will be dealt in the later posts.
- Filing Annual/Biannual reports (Which contain list of changes to the NDA/ANDA/MAA) with the regulatory agencies.
- Reporting any adverse effects which have occurred/may occur due to the use drug products.[12]
- Maintenance of the complete history of each Drug products (Filing history with agencies/customers, amendments, annual reports).
- Taking part in design and revision of drug product labels, packing leaflets.
- Taking part in the Formulation development process by advising the R & D scientists regarding various guidelines, laws and regulations.

Formats of Dossier includes CTD, e CTD, ACTD.

CTD – Common Technical Document[13]

The CTD has five modules

1. Administrative information and prescribing information.
2. Common technical document summaries.
3. Quality.
4. Nonclinical study reports.
5. Clinical study reports.

There are two categories of modules

- Regional module: 1 (different for each region; i.e., country).
- Common modules: 2–5 (common to all the regions).

The CTD defines the content only of the common modules. The contents of the Regional Module 1 are defined by each of the ICH *regions* (USA, Europe and Japan).

According to ICH the CTD falls under M4 part. CTD is an ICH standard that FDA adopted in a consensus process, as a member of ICH, together with other member regions, Europe & Japan.

eCTD – Electronic Common Technical Document

The electronic common technical document (eCTD) is an interface and international specification for the pharmaceutical industry to agency transfer of regulatory information through electronic way. Version of eCTD – an upgrade over the original CTD – was finalized on February 12, 2002.

ECTD is not a creation of FDA

XML-based eCTD Backbone replaces PDF Table of Contents.

ACTD – Asian Common Technical Document

The ACTD has four modules:

1. Administrative information and prescribing information
2. Quality
3. Nonclinical study reports
4. Clinical study reports

ACTD is followed by all the Asian countries.

Protocol for Dossiers

Please Note: Only Dossiers submitted in accordance with this protocol will be accepted

A few important reminders

- All AMCP dossiers will not be considered and the information submitted in AMCP format will not be included in the review.
- Submissions received that do not use the Evidence Submission Form (found at the end of this protocol) will not be accepted/reviewed. Additional information, other than the Drug Product Label, is not requested and will not be reviewed. Specifically, please refrain from submitting AMCP dossiers, drug monographs, or other such pre-made materials which generally include a broader base of information on the epidemiology, path physiology, diagnosis, clinical course, and burden of the disease.
- Only electronic submissions will be accepted. Submissions not received in an electronic format will not be reviewed.
- Please provide a cover letter with signature verifying the accuracy and veracity of the document, and a contact person who can answer questions and provide additional information regarding the submission materials.
- All information submitted to the Center for Evidence-based Policy may be available to the public. Any and all markings or statements of confidentiality shall be considered null and void.

MATERIALS AND METHODS

The Registration of a drug product is a tedious process followed in every Pharmaceutical Industry. The registration certificate, which is a mandatory document for doing the business further, is only given if the

manufacturer satisfies to every technical document submitted to the respective Drug Regulatory Authority. The lead challenges faced now-a-days during the registration is the types of queries raised after submission of dossier. The Research carried out with the collected data by analyzing the terms of the below parameters.

Methodology

Every study has some patterns and follows certain pathways in order to attain the goal. So, the method to be followed plays an important role in determining the outputs as well as the consequences of study.

Type of Study

- The Research was conducted with an objective to study and assess Regulatory requirements for the registration of Drug product in the world wide.
- The steps involved in responding to the Drug Regulatory Authority was also studied.

1) "The Drug Effectiveness Review Project Evidence Submission Protocol"

A format for submission of clinical evidence for systematic evidence-based reviews of drug classes. The standard protocol for submission of dossier is studied. Evidence submissions prepared under this protocol are submitted to and a copy retained by the Center. Information included in any submission is subject to use and/or reference in the report.

2) "Recent pharmaceutical patent decisions"

This article has a study about the patent infringement and its court decisions. The overall trend in patent law is the continued tension between the court of appeals for the patent rights. The main aim is to reduce the costly litigation by grounding the opponent opinion of the case law.

3) Guidance On Variations To A Prequalified Product Dossier

This guidance document was technically and structurally inspired by the "Guideline on dossier requirements for type IA and IB notifications"1. It is intended to provide supportive information on how to present an application to implement a change to a prequalified product.

4) Guidelines On Variations To A Registered Pharmaceutical Product

The requirements specified in the Guidelines have been adapted from the current WHO Guidance on Variations to a Prequalified Product. This guideline applies to applicants intending to make changes to the different sections of product dossiers for an API or an FPP of a registered pharmaceutical product. This guideline should be read in conjunction with other applicable guidelines including the Guidelines on submission of Documentation for Marketing Authorization of a Pharmaceutical Product for Human Use and its annexes.

RESULTS AND DISCUSSION

Dossier

Collection of documents containing the detailed information about technical data for human use. It is called as new drug application (NDA) in United states and Marketing Authorization approval (MAA) in Europe.

The lead challenge faced during the registration of drug product is the handling of queries for the final registration certificate for the product.

1) Finished Product
2) Active Pharmaceutical substance
3) Variation
4) Infringement.

Finished Product

A finished dosage form of a pharmaceutical product which has undergone all stages of manufacture including packaging in its final container and labeling.

What types of queries are raised in Finished Product?

a) License
b) Technical documents
c) Art work

License: Queries on.

- **Product license**

This is certified to maintain as a record to prove that the specified brand is the ownership of concerned industry. If there is a infringement or copy of the brand name then the query arises.

- **GMP – Good Manufacturing Practice**

There are two types of GMP followed in the industry they are Plant GMP and Product GMP. The queries are raised if the validity expires or if the plant GMP is uncertain of the product running plant.

- **COPP – Certificate of Pharmaceutical Product**

It is certified to ensure that the product is a pharmaceutical product for human use and it has no harm for the use. There are two types of COPP – With Q & Q and without Q & Q according to the client specification.

- **FSC**

Free sale certificate – this is given by the state drug authority to the pharmaceutical company for the free import and export of the product. The queries are generally because of the validity of the certificate or if the product falls under the NOC criteria

- **BE studies**

The bioequivalence studies gives the clinical data documents (Module 5) of a dossier. Mostly BE studies in Indian pharma companies are done by giving it outside to the other industries (to that of the reference product). The maximum timeline given for the query response regarding the BE studies are of 6 months.

Generally the queries are about the snapshots, shipment details of the product and majorly about the certificate from the IEC.

- **CDP**

Comparative Dissolution Profile:

In CDP there are 4 media where the following product is proved to be equivalent to that of Innovator product (p H 1.2, p H 4.5, p H 6.8 andwater).

This study is mainly done to compare the dissolution status of the product.

- **AMV**

Analytical Method Validation:
Assay, dissolution and related substance (impurities)

Studies are done on the precision, linearity, ruggedness, specificity and system suitability. Methods adopted for AMV are HPLC, HPTLC and other chromatogram studies.

For example
It was noted that the FPP analytical methods were adopted from BP monograph. Therefore you are requested demonstrate suitability of the related substances method to your product by means of analytical method verification studies.

- **Batch ManufacturingRecord**

This has a record of all the process of the product that is from the dispensing of the raw material till the coating process and its parameters. The final formula of the product is given in the BMR with the batch size production of the product.

- **Stabilitystudies**

For example
Please note that you submitted data only for long term stability condition (30±2˚C /65%±5%) for batches 10124003, 10195001 and 11124003 for a period of 36 months were submitted. You are therefore requested to submit accelerated stability data at (40±2˚C/ 75±5%) for not less than three batches for review.

- **PDR**

Pharmaceutical Development Report:
The study is initiated to prove the safety and stability of the product, it is the concise form of the Quality overall summary.

For example
Please note that pharmaceutical development report submitted was considered grossly insufficient. You are therefore requested to submit pharmaceutical development studies report with experimental data covering the following main headings:-

a) Details of quality target product profile for the developed product;
b) Discussion on the choice of excipients, in particular their functions and concentrations and compatibility of the API withexcipients;

Detailed information on development of unit and branch formulae of the product. Justification should be provided on the choice of dissolution method used in development studies specifically on its discriminatory capability:-

c) The selection and optimization of the manufacturing process, in particular its critical steps and process controlstrategy.
d) Tabulated summary of the compositions of the FPP batches (batch number, batch size, manufacturing date) used in bioequivalence studies, stability studies and processvalidation.

Selection of excepients

On the basis of API physical and characteristics and based on the result of compatibility studies. prototype formula was proposed which would be stable in HDPE bottle, the justification for inclusion of each excipient has been summarized.

Selection of suitable suspending agent

Colloidal silicon dioxide (heavy) and colloidal silicon dioxide (aerosol) xanthan gum The function of suspending agnet is to increasing the viscosity and their by slowing down and settling process.

Colloidal silicon dioxide is the most commonly used suspending agent.

Selection of viscosity modifier

Viscosity of the final formulation is important for the administration and stability of the product.

Selection of sweetening agent

Aspartame imparts sweet nature for the product which help to mask the bitterness of the formulation.

Selection of flavouring agent

Flavours are very important for the formulation especially when the product is ment for administration to children.

Strawberry flavor 17.41.0549 impart the necessary flavor for the formulation.

Art works

- **Item code**

For every individual pack size of the single product there will be a item code which will specify the whole details of the pack size. For example the item code will denote the dimensions, colour, type of materials used, language, specification etc.

GMP

- **Storageconditions**

According to the ICH there are four climatic zones classified with respective to their individual climatic conditions. The artwork should be given preferably 'should be stored below 30˚C or 25˚C'.

For example
A valid manufacturing licences or GMP certificates for the production of API at Delta Finochem Pvt. Lt, India. Certificate of Analysis

Certificate of Analysis
For example

SUMMARY AND CONCLUSION

This study reveals about the lead challenges faced by every pharmaceutical industry during the registration of drug product. The study observes that the problems are raised because of the improper notifications given to the Regulatory department from the Production department. It is because one person does the formulation of product which is the quality document, the other person handles the vendor document which is the Administrative document and the dossier is finally documentated by the person who is not related to any of the technical data's.

Major of the queries are questioned from the following parts:

1) Vendor documents.
2) Formulation documents.
3) Clinical documents.
4) Stability data.
5) Product information containing documents.
6) Because of this the queries are raised by the specific Ministry of health where the product is going to be registered. This can be overcome by maintaining a expertise person in every phase of technical data to cross verify, before the final format of dossier is made and sent to the MOH.

CONCLUSION

By overcoming all the above said problems during the submission of the dossier the boons which will faced by the Industry includes The on time registration of the drug product, No extra wages on the product for the resending the corrected dossier, Self reputation of the Industry, Good bond with the Ministry of health, Quick development of the product in the registered place. So it is the duty of each and every person who is handling in the preparation of dossier to check the technical documents with the requirements of the respective Ministry of health.

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