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STEPS TO BE FOLLOWED DURING REGISTARTION OF DRUG PRODUCT WITH CRITICAL PARAMETERS

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Abstract:

Registration of a drug product is a vital task in the world countries. The quality , safety and efficacy plays an important role during the drug registration process. For better treatment, and also for the best safety and efficacy of the drugs must be maintained and rationalize for public security. The requirements of drug products are harmonized in regulatory countries by common technical document. The main step is to know the detailed study about the dossier. The quality, safety and efficacy has its own role in the dossier. ICH brought regulatory authorities and pharmaceutical industries of Europe, Japan and Us. This paper approaches with the critical parameters during drug product registration in the form of dossier.

Keywords: *Dossier, Registration, Drug product, Critical parameters.*

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INTRODUCTION:

- What work is done in Regulatory Affairs Department?
- Regulatory Affairs Department of a pharmaceutical company files all the information related to the development, manufacture, control, stability studies, packing, labeling , safety and efficacy studies of drugs with the Regulatory agencies in a prescribed format as ANDA/NDA/MAA/DMF etc.
- 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).

"**The main document for Registration Certificate is a DOSSIER" [1]**

What is a dossier?

- Collection of documents containing the detailed information about technical data for human use is called a dossier. It is called as NDA (New drug application) in USA and MAA (Marketing authorization approval) in EU.

Why is a dossier needed?

- The main purpose of dossier is to get the registration certificate from the various countries for exploration of product.

When is a dossier done?

- Once the product studies is completed from the plant side and the product is headed for importing and exporting.

Formats of Dossier

There are three types and they are

- **CTD**
- **e CTD**
- **ACTD**
- **CTD – Common Technical Document** :
- Administrative information and prescribing information
- Common technical document summaries
- Quality
- Nonclinical study reports 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)

e CTD – 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 – Asean Common Technical Document

The ACTD has four modules:

- Administrative information and prescribing information
- Quality
- Nonclinical study reports Clinical study reports
- ACTD is followed by all the ASEAN countries. [3]

SCOPE AND OBJECTIVE:

Scope:

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.

Objective:

- To know the detailed study about the dossier submission.
- To learn about the general requirement regarding the dossier in every Ministry of Health.
- To up gain knowledge in preparing dossier without any chance of any future queries.
- To be an expertise in handling all the response of queries within the specific timelines.

RESEARCH METHODOLOGY [2]

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.

STUDY AND DISCUSSION:

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.

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.

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 and water).
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.

Batch Manufacturing Record:
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

Stability studies:
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

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.

Storage conditions
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'.

Active Pharmaceutical Ingredient:
A substance used in the FPP, intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings.

The major part of queries falling under Active Pharmaceutical Ingredient

- Working standard
- Specification
- Grade
- Stability
- GMP
- Certificate of analysis

What is variation?
Responsibility for the quality, safety and efficacy of medicinal product including both pharmaceutical and biological products lies first and foremost with the manufacturer/marketing authorization holder. A basic function of MOH is to evaluate the quality, safety and efficacy of medicinal products.

Article 81 and 82 of Drug Act respectively define that variation of any marketing authorization cannot be proceeded unless it obtains prior approval from MOH. Application for Variation shall be submitted by the marketing authorization holder.

Types of variation:
Minor Variation (Type I) Major Variation (Type II)
Types of Changes in the Variation: Administrative. Quality.
Safety and efficacy.

Minor Variation (MiV-N & MiV-PA)
Minor variations are changes that may have minor

effects on the overall safety, efficacy and quality of the FPP. Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the variation application.

There are two types are Minor Variation, they are

Minor Variation – Notification (Type IA)
'Do and Tell' – If the notification fulfills the requirements as per described under Miv-N, then the MOH shall acknowledge receipt of a valid notification.

Minor Variation – Prior Approval (Type IB)
If the application fulfills the requirements as per described under MiV-PA, the MOH shall issue an approval for the proposed change
Timeline – Within a duration as stated in MOH announcement following receipt of a valid application.

Major variation (MaV):

Major variations are changes that could have major effects on the overall safety, efficacy and quality of the FPP. The documentation required for the changes included in this reporting type should be submitted. Prior acceptance by NDA following presentation to the Licensing and Amendments Review Committee (LARC) is required before the changes can be implemented. A letter of acceptance will be issued for all major variations when the variation is considered acceptable. These variations will be handled within a time period of 90 working days.
Variation to a registered medicinal product in terms of administrative data and/or changes with minimal/no significant impact on the aspects of efficacy, quality, and safety.

Major Variation – Prior Approval (Type IIA)
If the application fulfills the requirements as per under MaV, the MOH shall issue an approval for the proposed change.

Timeline – Within a duration as stated in MOH announcement following receipt of a valid application.
Infringement:

What is infringement [3]?
An infringement is a minor offense that involves breaking a rule or a law. An infringement can also be a violation of a rule or an agreement that applies in a specific situation and results in penalties.
In other words it is defined as violation of an innovation of other's right such as invasion of an exclusive right of intellectual property.

What types of infringement occurs during the registration of drug product?

- Patent
- Trademark
- Copyright

PATENT INFRINGEMENT

Definition:
Patent infringement is the commission of a prohibited act with respect to a patented invention without permission from the patent holder. Permission may typically be granted in the form of a license. The definition of patent infringement may vary by jurisdiction, but it typically includes using or selling the patented invention.
Different types of infringement:

There are different ways another party may infringe on your patent, including:

- **Direct infringement:**
  - This occurs when a product covered by a patent is manufactured without permission.
- **Indirect infringement:**
  - An indirect infringer may induce infringement by encouraging or aiding another in infringing a patent.
- **Contributory infringement:**
  - This occurs when a party supplies a direct infringer with a part that has no substantial non- infringing use.
- **Literal infringement:**
  - This exists if there is a direct correspondence between the words in the patent claims and the infringing device.

TRADEMARK INFRINGEMENT [4]

What is trademark infringement?
Trademark infringement is the unauthorized use of a trademark or service mark on or in connection with goods and/or services in a manner that is likely to cause confusion, deception, or mistake about the source of the goods and/or services.
Infringement of Trademark
What amounts to Infringement of a Trademark?
Infringement of a Trademark in India means violation of the exclusive rights granted to the registered

proprietor under the Trademarks Act, 1999 to use the same in relation to the goods or services in respect of which the trademark is registered. Section 29 and Section 30 of the Trademark Act, 1999 lay down the provisions for protection of a registered trademark in case the same is infringed upon by a person not being a registered proprietor or licensee.

Section 29 of the Trademarks Act, 1999 provides that a registered trademark is infringed when a person not being a registered proprietor or licensee, uses in course of trade;

Laws governing Trademark Law in India:

Trademark Act, 1999

Trademark Rules, 2002

Trademark forms fees and cost in India

Trademark Rules, 2002 under Rules 11 and 12 provide for the regulations governing filing of fees and forms for the purpose of trademark prosecution in India.

FORM TM-1- Application to register a trademark for a specification of goods or services included in one class
FORM TM-2- Application to register a trademark for goods or services included in a class from a convention country
FORM TM-51- Application for the registration of a trademark for different classes of goods or services
FORM TM-52- Application for the registration of a trademark for different classes of goods or services from a convention country

- Application to register a trademark in one class has been increased from INR 3,500 toINR 4,000
- Application to expedite examination of a mark has been increased from INR 17,500 toINR 20,000
- Injunction:

A trademark owner can force a violator to stop using a mark that is confusingly similar to the owner's trademark by getting a court order called an injunction. The court order prohibits the infringer from continuing to use the infringing mark. If the infringer disobeys the court order, he can be held in civil contempt of court and fined. Fines for contempt of court are issued in addition to any other monetary penalties for trademark infringement.

Penalties:
The penalty for applying for unauthorized trademark:

For using unauthorized trademark, a person is punishable with imprisonment for a minimum of 6 months, which in certain cases can extend to 3 years.

On top of this, a fine of about fifty thousand rupees to a maximum of 2 lakh rupees is imposed on the infringer.

The penalty for selling product and services with an unauthorized trademark:

The punishment remains same for this as well, an imprisonment of not less than 6 month and can be extended to 3 years, along with a fine varying from 50 thousand to 3 lakh.

However, the punishment can be avoided if he/she proves that the infringement was out of unknowing means and an innocent act, also that he/she has taken all the necessary precautions for not violating the rights.

The penalty for claiming the trademark to be registered:

If a person claims to have registered a trademark on product and services which are not true, then there is a possibility of imprisonment for a tenure which may extend to 3 years or a fine, and in the worst scenario it can be both.

COPYRIGHT INFRINGEMENT [5]:
As per the Copyright Law in India, copyright subsists in all original published or unpublished literary, artistic works etc. Copyright comes into existence as soon as a work is created and no formality is required to be completed for acquiring copyright protection. However, it is advisable to apply for registration of Copyright in India for its evidentiary value.

The Copyright Law in India at present is governed by the Copyright Act,1957 along with the Copyright Rules, 2013. The first copyright legislation in India was the Indian Copyright Act, 1914 which was essentially based on the U.K. Copyright Act, 1911, and has borrowed extensively from the new Copyright Act of the United Kingdom of 1956.
India is a member of the Berne Convention of 1886 as well as the Universal Copyright Convention of 1951. Therefore, world created in other member states is accorded protection in India as well. Though India is not a member of the Rome Convention of 1961, WIPO copyrights Treaty (WCT) and the QIPO Performances and Phonograms Treaty (WPPT), the Copyright act is compliant with it. The 2012

amendments have made the Indian Copyright Law compliant with the WCT and WIPPT.

Copyright protection in India is granted in respect of literary, dramatic, musical and artistic works and produces of cinematograph films and sound recordings. It is essentially a bundle of rights including but not limited to rights of reproduction, communication to the public, adaptation and translation of the work.

Registration of copyright is not mandatory. However, it is advisable to apply for registration of Copyright as the certificate of registration of copyright and the entries

made therein serve as prima facie evidence in a court of law with reference to dispute relating to ownership of copyright. The Copyright Act of 1957, as amended in 2012.
Copyright filing forms in India

An Application for registration of Copyright is made on Form-XIV.

An Application for registration of changes in Particulars of Copyright is made on Form- XV An Application for the Relinquishment of Copyright is made on Form-1

Elements to infringe:

There are three elements that must be in place in order for the infringement to occur.

- The copyright holder must have a valid copyright.
- The person who is allegedly infringing must have access to the copyright work.
- The duplication of the copyrighted work must be outside the exceptions.

Penalties:
The legal penalties for copyright infringement are:

- Infringer pays the actual dollar amount of damages and profits.
- The law provides a range from $2000 to $150,000 for each work infringed.
- Infringer pays for all attorneys fees and court costs.
- The court can issue an injunction to stop the infringing acts.
- The court can impound the illegal works.
- The infringer can go to jail.

SUMMARY AND CONCLUSION:

SUMMARY:
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

- Vendor documents
- Formulation documents
- Clinical documents
- Stability data
- Product information containing documents

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 is

- 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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