PREPARATION OF DOSSIER FOR THE NEW FORMULATION AS PER ICH EU-CTD FORMAT: *A REVIEW*

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Introduction:

There are various regulatory authorities to regulate the market of pharmaceutical products. These regulatory agencies are responsible for the marketing authorization of pharmaceutical products. Pharmaceutical companies required to apply for the approval of marketing authorization of any new formulation (generic) after the innovator formulations. Then regulatory agencies decide to approved/reject formulations. Different regulatory agencies have been established for the same, UK-MHRA (United Kingdom Medicine and Healthcare Regulatory Agency) guidelines one of them. In this article dossier preparation for the approval of market authorization of new formulation reviewed as per European Common Technical Document (EU-CTD).

Preparation of dossier for the approval of market authorization of new formulation as per European Common Technical Document (EU-CTD) involve following different steps:

1. Study the format and Content of European Common Technical Document (EU-CTD) for U.K
2. To prepare dossier in the CTD format for new formulation for taking marketing authorization of same in E.U.

Methodology: [1-5]

1. Formulation and development:

Following studies need to be conducted for the preparation of dossier in the CTD format for taking market authorization of new formulation in E.U.

1. Different experimental R&D batches prepared for the proposed formulations and required to conduct accelerated stability at 40°C ± 2 and 75%RH ± 5%. Results obtained from the stability study for 6 months; should have no significant change in physical and chemical properties of the formulation for the approval. However, it is recommended to store the formulation below 25°C.
2. The compatibility of the excipients with the drug molecule needs to be studied. Formulation therefore, must be stable. Moreover, the drug substance (API) should not be susceptible to degradation in the recommended storage conditions. If the assigned shelf life of the API lies approx. 5 years, then there is no need to add overages in the preparation.
3. Compatibility between drugs and inactive ingredients also need to study. The tests, procedure and acceptances criteria adopted as per Ph. Eur and U.S.P for drug should ensure the quality of new formulation. The fixed specifications for residuals should be equal or less than those required in the corresponding ICH.

4. Analytical methods for the both assay and related substances to detect the degradation of the drug substances which may occur during stressed conditions i.e; Acid degradation (HCl) and Oxidization (H_2O_2).
5. Stability study under the stressed temperature and light condition
6. *In vitro* dissolution studies to meet the pharmacopoeia specifications for weight variation, assay, and content uniformity.
7. Bioavailability, Pharmacokinetic, and Bioequivalent studies in human.

Approval compliances:

For getting approval of market authorization the product must be stable under the accelerated conditions of 40 ± 2^0c/75%RH±5%RH. Furthermore, the results of long term study (E.U & Brazil for 6 months at 25 ± 2^0c/60%RH±5%RH & 30 ± 2^0c/70%RH±5%RH respectively) should suggest no significant increase in the level of impurity is estimated by the accelerated stability studies.

Result of *In vitro* dissolution studies for the formulation must meet the Ph. Eur. dissolution specifications; stating that not less than 85% of drug content should be released within 60 minutes.

The Bioavailability, Pharmacokinetic, and Bioequivalent studies also required to perform for filling of approval format. The bioavailability involves the total area under the plasma level versus time curve (AUC_{0-48}, $AUC_{0-\infty}$), peak plasma concentration (C_{max}) and time to C_{max} (T_{max}). No statistically significant difference should be found between the AUC, C_{max} and T_{max} values of the test and reference. The data need to be collected for the bioequivalence studies of proposed drug product and should fulfil the various requirements as per the MHRA and ICH guidelines; therefore, generic formulation should be bioequivalent with the innovator formulation.

2. Preparation of dossier in the CTD format for new formulation for taking marketing authorization of same in E.U.

2.1 Procedure for filing application to European Medicinal Agency (EMEA) approval for dossier

Application can be filed by two procedures

- Centralize procedure
- Decentralize procedure or mutual recognition procedure

2.2 Method for obtaining EMEA approval

- Submitting an application to get marketing authorization.
- Submitting a corresponding European dossier.
- Obtain mutual recognition from concerned state about the drug need to file.

3. Collection of data and development of a formula containing active ingredient.

Before commencing to file a dossier a formula is required to which application for the marketing authorization will be filed. Such collection is based on the similar formulation and technology was used in reference product.

- Active ingredients: Collection of data as same quality and quantity as of innovator product.
- Inactive ingredients: The data will be collected for the drug for which patent has expired and which is similar to innovator product.
- Technology: Same or almost identical technology will be chosen for formulation.

4. Collection of data to show product biostudy:

According to requirement in filing of bridged product approval data which show that product will be bioequivalent to innovator product. For such purpose data will be collected to show bioeqivalancy.

Data of C_{max} T_{max} and AUC will also be collected to show bioeqivalancy of product.

5. Filling of application form:

The objective of this step is to determine the need of data in filling application form. In order to get authorization filling of application form is a requirement of MHRA (Medicine and Healthcare Regulatory Agency) together with the Dossier. The form for marketing authorization is available on site of MHRA.

6. Preparation of corresponding European dossier

Contents for European dossier preparation are divided in two parts

PART I

SUMMARY OF THE DOSSIER

A. Administrative data

B. Summary of product characteristics

C. Expert reports

PART II

Chemical, pharmaceutical and biological testing of medicinal products

7. Collection and presentation of administrative data:

Data will be collected related to the medicinal product which is the subject of the application name of the active substance, name and address of the applicant together with the name and address of the manufacturers and the sites involved in the different stages of the manufacture including the manufacturer of the finished product, the manufacturer of the active substance and name and address of the importer. Number of volumes of documentation submitted in support of the application, product information will be given according to guideline of European Medicinal Agency (EMEA).

Summary and Conclusion:

In the present work preparation and submission of dossier according to UK-MHRA (United Kingdom Medicine and Healthcare Regulatory Agency) guidelines reviewed. Dossier preparation studied as per ICH EU-CTD format. It is evident from this filling method is simple than the traditional method of filling. Because traditional format was very lengthy and time-consuming process, but after 2003 three countries started CTD format EU, USA and Japan. So we can file in easy way.

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