GUIDANCE FOR INDUSTRY

ON

Requirement of Chemical & Pharmaceutical Information including Stability Study Data Before Approval of Clinical Trials / BE Studies

DRAFT GUIDANCE

This guidance document is for feedback purposes only

Comments and suggestions regarding this draft document should be submitted within 30 days of publication, to

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CENTRAL DRUGS STANDARD CONTROL ORGANIZATION

DIRECTORATE GENERAL OF HEALTH SERVICES

MINISTRY OF HEALTH & FAMILY WELFARE

GOVT. OF INDIA

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1 ABBREVIATIONS AND DEFINITIONS

API	Active Pharmaceutical Ingredient
BA	Bio-availability
BE	Bio-equivalence
CDSCO	Central Drugs Standard Control Organization
CT	Clinical Trial
FDC	Fixed Dose Combination
GMP	Good Manufacturing Practices
GC	Gas Chromatography
HPLC	High Performance Liquid Chromatography
INN	International Non-proprietary Name
IR	Infrared
NDA	New Drug Application
NMR	Nuclear Magnetic Resonance
PK / PD	Pharmacokinetic and Pharmacodynamic
NOC	No objection certificate
UV	Ultraviolet

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GUIDANCE FOR INDUSTRY ON REQUIREMENT OF STABILITY STUDY DATA BEFORE APPROVAL OF CLINICAL TRIAL / BE STUDIES

3 BACKGROUND

Demonstration of safety and efficacy of the drug product for use in humans is essential before the drug product can be approved for import or manufacturing and marketing in the country. The Rules 122A, 122B and 122D, 122 DA, 122DAA, 122E of Drugs and Cosmetics Rules and Appendix I, IA and VI of Schedule Y, describe the information/data required for approval of clinical trial and/or to import or manufacture of new drug for marketing in the country.

No clinical trial for a new drug, whether for clinical investigation or any clinical experiment by any institution, shall be conducted except under, and in accordance with, the permission, in writing, of the Licensing Authority defined in clause (b) of Rule 21.

Application for Clinical trial is to be made in Form 44 accompanied with requisite fees and documents pertaining to chemical and pharmaceutical information, animal pharmacology and toxicology data, safety & efficacy data generated on human, regulatory status in other countries etc. as per Appendix I of Schedule Y to Drugs & Cosmetic Rules.

The chemical and pharmaceutical information required to be submitted alongwith the clinical trial applications are specified in item nos. 2.1, 2.3, 2.6 and 2.7 of Appendix I.

While adequate chemical and pharmaceutical information should be provided to ensure the proper identity, purity, quality & strength of the investigational product, the amount of information needed may vary with the Phase of clinical trials, proposed duration of trials, dosage forms and the amount of information otherwise available.

This guidance document has been prepared to specify the requirements for submission of chemical and pharmaceutical information including stability study data for approval of clinical trial / BA-BE studies. This guidance will ensure that sufficient data is submitted to CDSCO to assess the safety as well the quality of the proposed clinical trials from chemical and pharmaceutical information perspective.

4 SCOPE

These guidelines apply to approval of clinical trial and BA / BE study of various categories of new drug formulations which are considered as new drug as per Rule 122E of Drugs and Cosmetics Rules.

This guideline does not apply to biologicals and vaccines.

5 General Consideration:

This guideline is based on regulatory requirements for approval of clinical trial of new drugs in India as prescribed under Drugs and Cosmetic Rules. For manufacture of trial batches of new drug for clinical trials in India, the applicant is required to obtain licence in

Form-29 from the concerned State Licensing Authority based on NOC obtained from CDSCO. Test batches of new drugs for development and generation of data of any new drug should be manufactured only after obtaining the licence in Form-29.

6 Chemical and Pharmaceutical information including stability data required to be submitted for approval of clinical trials (Phase-I/II/III/IV) and BA / BE studies.

Chemical and pharmaceutical information including:

Information on active ingredients:

i. Drug information (Generic Name, Chemical Name or INN) & physicochemical data including chemical name and structure, empirical formula and molecular weight

Information on the nomenclature of the drug substance should be provided. For example Recommended International Non-proprietary Name (INN), Chemical name(s), Company or laboratory code.

The structural formula, molecular formula, and the molecular weight should be provided.

ii. Analytical Data

Confirmation of structure based on spectral analyses should be elucidated by various means which may include Elemental analysis, Mass spectrum, NMR spectra, IR spectra and UV spectra.

Polymorphic identification-If the drug substance exists in more than one crystalline form data on polymorphic identification should be provided.

iii. Stability Studies

Data supporting stability in the intended container closure system for the duration of the clinical trial is required to be submitted.

As per schedule Y of the Drugs & Cosmetics Rules, stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The types of studies conducted, protocols used, and the results of the studies should be summarized. Full long term stability data is not required at the time of filing, provided some preliminary stability data is available together with a commitment that the stability of the clinical trial samples will be monitored according to the stability protocol until the shelf-life has been established. A summary of the stability protocol (e.g. tabular format,

summarizing frequency of testing, tests to be conducted etc.) should be provided.

Phase I Trial: The applicants are expected to submit whatever Stability study data available with them for obtaining permission for Phase I trial.

Phase II Trial: Stability data for the clinical materials used in the Phase I study should be provided. The applicant shall submit minimum one month accelerated as well as Real time stability study data while applying for Phase II trial with a commitment that stability study data will be provided at required intervals as and when data becomes available. Stability study for clinical material used in Phase II should be provided on quarterly basis in tabular format as soon as the data become available. The submitted information should include the Batch No., manufacturing site, date of manufacturing and relevant information of drug substance used (Lot No., manufacturer) used to manufacture the product. In case there is a significant change during the stability studies, it shall be reported immediately within 10 days to the Licensing Authority.

Phase III Trial: Stability data for the clinical materials used in the Phase II studies should be provided. The applicant shall submit minimum one month accelerated as well as Real time stability study data in respect of trial batches to be used in the Phase III clinical trial with a commitment that stability study data will be provided at required intervals as and when data becomes available. Stability study for clinical material used in Phase III should be

provided on quarterly basis in tabular format as soon as the data become available. The submitted information should include the Batch No., manufacturing site, date of manufacturing and relevant information of drug substance (Lot No., manufacturer) used to manufacture the product. In case there is a significant change during the stability studies, it shall be reported immediately within 10 days to the Licensing Authority.

iv. Impurities

For Phase I Clinical Trial Applications -
The structure (or other identifier, if not structurally characterized) as well as the origin should be included in the drug substance impurity table.

For Phase II and III Clinical Trial Applications -
The impurity name (or identifier), structure (if characterized) and origin should be provided in the table for all specified impurities.
Impurity levels for previously manufactured nonclinical and clinical batches may also be summarized within this section.

Data on Formulation:

i. Dosage form

The description of the dosage form should include the physical description, available strengths as well as any other distinguishable characteristics.

ii. Composition, Master manufacturing formula, Details of the formulation (including inactive ingredients)

List of all components of the dosage form, their amount on a per unit basis (including overages, if any) and a reference to their quality standards (e.g., Pharmacopeial monographs or manufacturer's specifications);

The composition should express the quantity of each component on a per unit basis (e.g., mg per tablet, mg per mL, mg per vial, etc.) and percentage basis including a statement of the total weight or measure of the dosage unit.

iii. In process quality control check-

A summary of in-process controls and process parameters should be provided. The critical steps, process controls, intermediate tests and final product controls should be identified and described in additional detail.

This information is not required to be submitted for Phase I & II clinical trial applications

iv. Finished product specification

Specifications for Phase II clinical trial applications are considered interim as they are based on a limited number of development batches. However, final specification should be submitted along with Phase III clinical trial application.

This information is not required to be submitted for Phase I clinical trial application

v. Method of Analysis

A brief description of the analytical methods used for the drug product should be provided for all tests included in the drug product specifications (e.g. reverse-phase HPLC, GC, etc.). Detailed descriptions of the step-by-step analytical procedures may be submitted wherever required by CDSCO.

This information is not required to be submitted for Phase I clinical trial application

vi. Excipient compatibility study

Results of the excipient compatibility study should be submitted for Phase II & III clinical trial applications

vii. Validation of the analytical method

Suitability of the analytical methods and a tabulated report of the validation information should be provided (i.e. results or values for specificity, linearity, range, accuracy, precision, robustness, limit of detection and limit of quantitation, where applicable).

This information is not required to be submitted for Phase I clinical trial application

viii. Stability Studies:

Data supporting stability in the intended container closure system for the duration of the clinical trial.

As per schedule Y of the Drugs & Cosmetics Act, stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. In case of formulations the testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system).

It is to be clarified that the product shall remain stable as long as CT/BE study is carried out which shall be justified by the firm before obtaining the permission.

If full term stability study data supporting shelf life is not available at the time of filing, a commitment shall be provided by the firm that the stability of the clinical trial samples, or samples considered representative of the clinical batches, will be monitored throughout the duration of the clinical trial. A summary of the stability protocol (e.g. tabular format, summarizing frequency of testing, tests to be conducted etc.,) should be provided.

Phase I Trial: The applicants are expected to submit whatever Stability study data available with them for obtaining permission for Phase I trial.

Phase II Trial: Stability data for the clinical materials used in the Phase I study should be provided. The applicant shall submit minimum one month accelerated as well as Real time stability study data while applying for Phase II trial with a commitment that stability study data will be provided at required intervals as and when data becomes available. Stability study for clinical material used in Phase II should be provided on quarterly basis in tabular format as soon as the data become available. The submitted information should include the Batch No., manufacturing site, date of manufacturing and relevant information of drug substance used (Lot No., manufacturer) used to manufacture the product. In case there is a significant change during the stability studies, it shall be reported immediately within 10 days to the Licensing Authority.

Phase III Trial: Stability data for the clinical materials used in the Phase II studies should be provided. The applicant shall submit minimum one month accelerated as well as Real time stability study data in respect of trial batches to be used in the Phase III clinical trial with a commitment that stability study data will be provided at required intervals as and when data becomes available. Stability study for clinical material used in Phase III should be provided on quarterly basis in tabular format as soon as the data become available. The submitted information should include the Batch No., manufacturing site, date of manufacturing and relevant

information of drug substance (Lot No., manufacturer) used to manufacture the product. In case there is a significant change during the stability studies, it shall be reported immediately within 10 days to the Licensing Authority.

Note 1: It may be clarified that chemical and pharmaceutical data required to be submitted for BA/BE studies of an unapproved new drug will be same as required for phase III clinical trial.

However, in case of application for BE permission of a drug already approved in the country, chemical and pharmaceutical data required to be submitted include Dosage form and its composition, master manufacturing formula, stability study data (as required for Phase III clinical trial).