GUIDANCE FOR INDUSTRY

ON

FIXED DOSE COMBINATIONS

(FDCs)

DRAFT GUIDANCE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

CDSCO, FDA Bhavan

Kotla Road, New Delhi – 110002

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

1.1 Abbreviations

API	Active Pharmaceutical Ingredient
BA	Bio-availability
BE	Bio-equivalence
CRF	Case Record Form
CT	Clinical Trial
FDC	Fixed Dose Combination
ICF	Informed Consent Form
IND	Investigational New Drug
INR	Indian National Rupee
LD	Lethal Dose
PK / PD	Pharmacokinetic and Pharmacodynamic

1.2 Glossary

Fixed Dose Combinations

Fixed Dose Combinations (FDCs) refer to products containing two or more active ingredients used for a particular indication(s).

2 TABLE OF CONTENTS

GUIDANCE FOR INDUSTRY
FIXED DOSE COMBINATIONS (FDCs)

3 BACKGROUND

The development of FDCs is becoming increasingly high either to improve compliance or to benefit from the added effects of the two or more active drugs given together. They are being used in the treatment of a wide range of conditions and are particularly useful in the management of chronic conditions.

FDCs should always be based on convincing therapeutic justification. Each fixed dose combination should be carefully justified and clinically relevant (e.g. in cases when each component of the FDC has several possible dosages, dosages that have shown benefit on clinical outcomes may be preferable).

Appendix VI of Schedule Y (Drugs & Cosmetics Rules 1945) specifies the requirements for approval for marketing of various types of FDCs. The same is further elaborated to provide a detailed guidance for industry.

4 SCOPE

These guidelines apply to manufacture / import and marketing approval of FDCs as a finished pharmaceutical product considered as new drug as per Rule 122(E) of Drugs and Cosmetics Act & Rules.

5 GENERAL CONSIDERATIONS

- A clear justification with a valid therapeutic rationale of the particular combination of active substances proposed will be the basis of approval.
- It is not always necessary to generate new (original) data. Evidence may be obtained from the scientific literature, subject to its being of adequate quality.
- In case of FDC where all the active ingredients are approved individually, if a Clinical Trial (CT) is required, confirmatory studies to prove efficacy, preferably by parallel group comparisons in which the FDC is compared to its individual substances may be considered. When feasible, a placebo arm may be incorporated. Comparative CTs of the FDC with reference treatment may be necessary, especially when the therapeutic justification talks more on the FDCs superiority over a reference treatment.
- An application for a marketing authorization may comprise:
    - Entirely original data.
    - Entirely data from the literature.
    - Both original data and data from the literature ("hybrid").

  For FDCs, it is likely that hybrid submissions will be the most common type.
- Chemical and pharmaceutical data should be always totally original, unless there is sufficient justification with literature when partial data can be in-original.

- Treasury Challan: of INR 15,000 if all active ingredients are approved in India for more than one year, or INR 50,000 in case any of the active ingredients is unapproved or approved for less than one year. However, a Challan of only INR 15,000 is required, in case the applicant has already submitted an application along with a Challan of INR 50,000 towards any of the single active ingredient approval, which is less than 1 year old.

- Any test batch/trial batch of new drugs for test and analysis purpose should be manufactured after obtaining Licence in Form 29 from the concerned State Licensing Authority and copy of the licence should be submitted alongwith the application for seeking permission to manufacture and market the new drug.

6 GUIDELINES ON DATA REQUIRED FOR APPROVAL FOR MARKETING FDCs

FDCs can be divided into the following groups and data required for approval for marketing is described below:

6.1FDC - Not marketed in India & one or more active ingredient(s) is a new drug not approved in India.

CLARIFICATION:

Such type of FDCs can be further classified into two categories as follows:

Category I:

One of the ingredients of the combination is an Investigational New Drug (IND). For such FDCs to be approved for marketing, data required to be submitted will be similar as per Appendix I of Schedule Y which is similar to data required for any new chemical entity (NCE).

For such FDCs the clinical trials is required to be carried out right from Phase I. For new drug permission of such FDCs the documents required to be submitted are as follows:

1. Form 44
2. Treasury Challan of INR 50,000.
3. Rationale for combining them in the proposed ratio and therapeutic justification along with supporting literature.
4. Source of bulk drugs /raw materials. For those ingredients which are approved and considered new drugs - If the applicant has a manufacturing license for bulk drugs, please

provide a copy of the same. Otherwise, provide the consent letter from the approved source regarding supply of material.

Clarification: In case if the applicant does not have an approval from DCGI to manufacture any of the Active Pharmaceutical Ingredient (API) which is considered as new drug, applicant can,

- Import the API → Applicant has to file separate application in Form-44 alongwith treasury challan and all relevant documents and comply with further requirements for import of API
- Manufacture the API → Applicant has to file separate application in Form-44 alongwith treasury challan and all relevant documents and comply with further requirements for manufacture of API
- Obtain the API from another manufacturer which is not yet approved by DCGI → In such case, the respective manufacturer of the API has to file an application separately in Form 44 along with treasury challan of requisite amount with all relevant documents. Such application will be processed simultaneously with the application for the FDC. Approval of the FDC will be considered after approval of the API.

5. Chemical and pharmaceutical information including:

a) **Information on active ingredients:**

Drug information (Generic Name, Chemical Name or INN) & Physicochemical Data including:

i. Chemical name and Structure - Empirical formula, Molecular weight
ii. Physical properties - Description, Solubility, Rotation, Partition coefficient, Dissociation constant
iii. Analytical Data: Elemental analysis, Mass spectrum, NMR spectra, IR spectra, UV spectra, Polymorphic identification
iv. Complete monograph specification including: Identification, Identity/quantification of impurities, Enantiomeric purity, Assay
v. Validations: Assay method, Impurity estimation method, Residual solvent/other volatile impurities (OVI) estimation method
vi. Stability Studies (refer Appendix IX of Schedule Y): Final release specification, Reference standard characterization, Material safety data sheet.

b) **Data on Formulation:**

i. Dosage form,
ii. Composition,
iii. Master manufacturing formula,
iv. Details of the formulation (including inactive ingredients),
v. In process quality control check,
vi. Finished product specification & Method of Analysis,
vii. Excipient compatibility study,
viii. Validation of the analytical method.
ix. Comparative evaluation with international brand(s) or approved Indian brands, if applicable.

x. Pack presentation ,
xi. Dissolution ,
xii. Assay ,
xiii. Impurities ,
xiv. Content uniformity ,
xv. pH ,
xvi. Force degradation study ,
xvii. Stability evaluation in market intended pack at proposed storage conditions ,
xviii. Packing specifications ,
xix. Process validation.

6. **Animal Pharmacology**

- Summary
- Specific pharmacological actions
- General pharmacological actions
- Follow-up and Supplemental Safety Pharmacology Studies
- Pharmacokinetics: absorption, distribution; metabolism; excretion

7. **Animal Toxicology**

- General Aspects
- Systemic Toxicity Studies
- Male Fertility Study
- Female Reproduction and Developmental Toxicity Studies
- Local toxicity
- Allergenicity/Hypersensitivity
- Genotoxicity

- Carcinogenicity

8. **Human / Clinical pharmacology (Phase I)**
   - Summary
   - Specific Pharmacological effects
   - General Pharmacological effects
   - Pharmacokinetics, absorption, distribution, metabolism, excretion
   - Pharmacodynamics / early measurement of drug activity

9. **Therapeutic exploratory trials (Phase II)**
   - Summary
   - Study report(s) as given in Appendix II

10. **Therapeutic confirmatory trials (Phase III)**
    - Summary
    - Individual study reports with listing of sites and Investigators.

11. **Special studies**
    - Summary
    - Bio-availability / Bio-equivalence.
    - Other studies e.g. geriatrics, paediatrics, pregnant or nursing women

12. **Regulatory status in other countries**
    - Countries where the drug is
        i. Marketed

ii. Approved

iii. Approved as IND

iv. Withdrawn, if any, with reasons

- Restrictions on use, if any, in countries where marketed /approved
- Free sale certificate (FSC) or Certificate of Pharmaceutical Product (COPP), as appropriate.

13. **Prescribing information**

- Proposed full prescribing information containing the following information:

14. **Samples and Testing Protocol/s**

- Samples of pure drug substance and finished product (an equivalent of 50 clinical doses, or more number of clinical doses if prescribed by the Licensing Authority), with testing protocol/s, full impurity profile and release specifications.

NOTE: Details of Animal Pharmacology & Animal Toxicology studies required to be carried out will be as per Appendix IV & Appendix III of Schedule Y of Drugs and Cosmetics Rules respectively.

Depending upon the nature of new drugs and disease(s) specific additions/deletions may be made to the above requirements.

Category II:

One or more of the ingredients of the combination is a New Drug not approved individually in the country however the same is approved in other country.

If such FDC is marketed abroad Phase III clinical trials are required to be conducted in India. In case, such a combination is not marketed anywhere in the world, clinical trials right from Phase I as appropriate are required to be conducted in the country.

For such FDCs to be approved for marketing, data to be submitted will be similar to data required for any new drug substance as mentioned in Category I above.

(In case of injectable formulation, sub-acute toxicity data conducted with the applicants' product has to be provided).

6.2 FDC - Not marketed in India but the active ingredients are approved/ marketed individually & it is likely to have significant PK/PD interactions

CLARIFICATION:

This group of FDCs includes those in which active ingredients already approved /marketed individually are combined for the first time (for marketing in India), for a particular claim and where the ingredients are likely to have significant interaction of a pharmacokinetic or pharmacodynamic (PK/PD) nature. This can be further classified in to following,

6.2.1 FDC - Marketed abroad

CLARIFICATION:

This group of FDCs includes those in which active ingredients already approved/ marketed individually are combined for the first time, for a particular claim and where the ingredients are likely to have significant PK/PD interaction, but, are being marketed abroad with an established safety and efficacy in humans.

For approval of such FDCs, following documents have to be submitted,

1. Form 44
2. Treasury Challan of INR 15,000 if all active ingredients are approved in India for more than one year, or INR 50,000 in case any of the active ingredients is approved for less than one year.

3. Complete chemical and pharmaceutical data (As per Annexure I)
4. Rationale for combining them in the proposed ratio and therapeutic justification along with supporting literature.
5. Summary of Drug-Drug-Interactions (known and/or expected) among the active ingredients present in the FDC, along with its implications. This should be prepared and signed by a competent person on behalf of applicant.
6. Clinical trials data showing safety and efficacy of the FDC in the same strength (that has been carried out in other countries) including published data.
7. In case of injectable formulation, sub-acute toxicity data conducted with the applicants' product has to be provided.
8. The regulatory status of the FDC in other countries.
   a. Countries where the drug is,
      - Marketed
      - Approved
      - Approved as IND
      - Withdrawn, if any, with reasons
   b. Restrictions on use, if any, in countries where marketed /approved
   c. Free sale certificate/ certificate of pharmaceutical product from the country of origin (in case of import of the finished form of the FDC).
   d. Copy Package Inserts, promotional literatures of FDC circulated in those countries where it is marketed.

NOTE*: Names of the countries where the FDC is Approved / Marketed / Withdrawn etc should be clearly stated in the covering letter also.*

9. Source of bulk drugs /raw materials (for those ingredients which are considered new drugs) - If the applicant has a manufacturing license for bulk drugs, please provide a copy of the same. Otherwise, provide the consent letter from the approved source regarding supply of material.

   Clarification: In case if the applicant does not have an approval from DCGI to manufacture any of the Active Pharmaceutical Ingredient (API) which is considered as new drug, applicant can,

   - Import the API → Applicant has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents and comply with further requirements for import of API
   - Manufacture the API → Applicant has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents and comply with further requirements for manufacture of API
   - Obtain the API from another manufacturer which is not yet approved by DCGI → In such case, the respective manufacturer of the API has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents. Such application will be processed simultaneously with the application for the FDC. Approval of the FDC will be considered after approval of the API.

10. Copy of proposed Package Insert (generic name of all active ingredients; composition; dosage form/s, indications; dose and method of administration; use in special populations; contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions) and draft Label / Carton etc.

6.2.2 FDC - Not marketed anywhere but individual components used concomitantly

CLARIFICATION:

FDC is not marketed anywhere in the world, but the individual components [active drug(s)] are already in use concomitantly (not as an FDC but individually) for the said claim.

For approval of such FDCs, following documents have to be submitted,

1. Form 44
2. Treasury Challan of INR 15,000 if all the active ingredients are approved in India for more than one year, or INR 50,000 in case any of the active ingredients is approved for less than one year.
3. Complete chemical and pharmaceutical data (As per Annexure I)
4. Rationale for combining them in the proposed ratio and therapeutic justification along with supporting literature.
5. Summary of Drug-Drug-Interactions (known and/or expected) among the active ingredients present in the FDC, along with its implications. This should be prepared and signed by a competent person on behalf of applicant.
6. Summary of available pharmacological, toxicological and clinical data on the individual ingredients
7. Clinical data showing safety and efficacy of the FDC / Concomitant use of the ingredients, in the same strength, including published data. If enough supportive literatures are

not available, then 'adequate evidence' on safe and effective concomitant use of the ingredients should be provided.

8. In case of injectable formulation, sub-acute toxicity data conducted with the applicants' product has to be provided.

9. Source of bulk drugs /raw materials (for those ingredients which are considered new drugs) - If the applicant has a manufacturing license for bulk drugs, please provide a copy of the same. Otherwise, provide the consent letter from the approved source regarding supply of material.

   Clarification: In case if the applicant does not have an approval from DCGI to manufacture any of the API which is considered as new drug, he can

   - Import the API → Applicant has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents and comply with further requirements for import of API
   - Manufacture the API → Applicant has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents and comply with further requirements for manufacture of API
   - Obtain the API from another manufacturer which is not yet approved by DCGI → In such case the respective manufacturer of the API has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents. Such application will be processed simultaneously with the application for the FDC. Approval of the FDC will considered after approval of the API.

10. Copy of proposed Package Insert (generic name of all active ingredients; composition; dosage form/s, indications; dose and method of administration; use in special populations; contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions) and draft Label / Carton etc.

6.2.3 FDC - Not marketed and individual components are not used concomitantly

CLARIFICATION:

In case the FDC is not marketed anywhere in the world and the individual components are not concomitantly used in routine clinical practice and the ingredients are likely to have significant PK/PD interaction, clinical trials may be required.

For obtaining permission to carry out Bio-availability/Bio-equivalence (BA/BE) studies (when applicable) followed by Clinical trial in Indian subjects with such FDCs, following documents have to be submitted to this office,

A. Form 44 (Application for manufacture and market New FDC, BA/BE study and clinical trial application)

B. Treasury Challan of INR 15,000 in case all the active ingredients are approved in India for more than one year, or INR 50,000 in case any of the active ingredients is approved for less than one year.

C. Appropriate chemical and pharmaceutical data (As per Annexure I a)

D. Rationale for combining them in the proposed ratio and therapeutic justification along with supporting literature.

E. Summary of Drug-Drug-Interactions (expected interactions, based on the pharmacology of active ingredients) among the active ingredients present in the FDC, along with its implications. This should be prepared and signed by a competent person on behalf of applicant.

F. Acute toxicity data (LD 50) and pharmacological data should be submitted.

G. In case of injectable formulation, sub-acute toxicity data conducted with the applicants' product has to be provided.

H. Source of bulk drugs /raw materials (for those ingredients which are considered new drugs) - If the applicant has manufacturing license for bulk drugs, please provide a copy of the same. Otherwise provide the consent letter from the approved source regarding supply of material.

Clarification: In case if the applicant does not have approval from DCGI to manufacture any of the API which is considered as new drug, he can

- Import the API → Applicant has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents and comply with further requirements for import of API
- Manufacture the API → Applicant has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents and comply with further requirements for manufacture of API
- Obtain the API from another manufacturer which is not yet approve by DCGI → In such case the respective manufacturer of the API has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents. Such application will be processed simultaneously with the application for the FDC. Approval of the FDC will considered after approval of the API.

I. BA/BE study protocol (when applicable), and Clinical study protocol as per Appendix X of Schedule Y

J. Patient Information Sheet and Informed Consent Form (ICF) as per Appendix V of Schedule Y

K. Copy of 'Ethics Committee' approval letters (if available)

L. Case Record Form (CRF)

M. Undertaking by Investigator(s) as per Appendix VII of Schedule Y and CV

N. Certificate of analysis of study drug(s)

O. Summary of available pharmacological, toxicological and clinical data on the individual ingredients should be submitted along with any published data.

After the successful completion of clinical trial(s) following documents have to be submitted to complete the marketing application,

1. Complete chemical and pharmaceutical data (As per the Annexure I)

2. Source of bulk drugs /raw materials (for those ingredients which are considered new drugs) - If the applicant has obtained permission for manufacturing of bulk drugs provide a copy of the same, otherwise provide the consent letter from the approved source, regarding supply of material.

   Clarification: In case if the applicant did not have approval from DCGI to manufacture any of the API which is considered

as new drug, he should submit all required data for grant of permission to Import /manufacture of the API.

3. BA/BE study report and Clinical Study Report conducted in Indian population as per Appendix II of Schedule Y. The study report should be certified by each of the participating investigator(s) in the study and the certification should acknowledge the contents of the report, the accurate presentation of the study as-undertaken, and express agreement with the conclusions. Each page should be numbered.
4. Copy of proposed Package Insert (generic name of all active ingredients; composition; dosage form/s, indications; dose and method of administration; use in special populations; contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions) and draft Label / Carton etc.

6.3 FDC - Marketed in India but some changes are sought

CLARIFICATION:

This group of FDCs includes those which are already marketed, but now it is proposed either to change the ratio of active ingredients or to make a new therapeutic claim or a new dosage form.

For approval of such FDCs, following documents have to be submitted,

1. Form 44
2. Treasury Challan of INR 15,000 in case all the active ingredients are approved in India for more than one year, or INR 50,000 in case any of the active ingredients is approved for less than one year
3. Complete chemical and pharmaceutical data (As per Annexure I)
4. Rationale for combining them in the proposed ratio/new dosage form and therapeutic justification along with supporting literature.
5. Summary of Drug-Drug-Interactions (known and/or expected) among the active ingredients present in the FDC, along with its implications. This should be prepared and signed by a competent person on behalf of applicant.
6. Clinical trials data showing safety and efficacy of the FDC with the proposed new claims including published data.
7. In case of injectable formulation, sub-acute toxicity data conducted with the applicants' product has to be provided.
8. The regulatory status of the FDC with the proposed new claims, in other countries.

a. Countries where the drug is Marketed / Approved / Approved as IND / Withdrawn, if any, with reasons

b. Restrictions on use, if any, in countries where marketed or approved

c. Free sale certificate/ certificate of pharmaceutical product from the country of origin (in case of import of the finished form of the FDC).

9. Copy of earlier approval from the DCGI for the FDC for which new claim is being proposed as new strength / indications / dosage form etc. In case the applicant is not having the approval for the said FDC, then the applicant has to provide details on source of bulk drugs /raw materials (for those ingredients which are considered new drugs) - If the applicant has manufacturing license for bulk drugs, please provide a copy of the same. Otherwise, provide the consent letter from the approved source regarding supply of material.

Clarification: In case if the applicant does not have approval from DCGI to manufacture any of the API which is considered as new drug, he can

- Import the API → Applicant has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents and comply with further requirements for import of API
- Manufacture the API → Applicant has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents and comply with further requirements for manufacture of API

- Obtain the API from another manufacturer which is not yet approve by DCGI → In such case the respective manufacturer of the API has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents. Such application will be processed simultaneously with the application for the FDC. Approval of the FDC will considered after approval of the API.

10. Copy of proposed Package Insert (generic name of all active ingredients; composition; dosage form/s, indications; dose and method of administration; use in special populations; contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions) and draft Label / Carton etc.

NOTE: Permission will be granted depending upon the nature of the claim and data submitted. A clinical trial/ BABE study may be required if the justification provided for the new claim(s) is not satisfactory.

6.4 FDC - Only for convenience

CLARIFICATION:

This group of FDC includes those whose individual active ingredients (or drugs from the same class) have been widely used in a particular indication(s) for years, their concomitant use is often necessary and no claim is proposed to be made other than convenience and should have demonstrated stability with no significant PK/PD interaction among the ingredients.

For approval of such FDCs, following documents have to be submitted,

1. Form 44
2. Treasury Challan of INR 15,000 if all the active ingredients are approved in India for more than one year, or INR 50,000 in case any of the active ingredients is approved for less than one year.
3. Complete chemical and pharmaceutical data (As per Annexure I)
4. Rationale for combining them in the proposed ratio and therapeutic justification along with supporting literature.
5. Summary of data showing NO significant PK/PD interaction among the ingredients. This should be prepared and signed by a competent person on behalf of applicant.
6. Summary of available pharmacological, toxicological and clinical data on the individual ingredients
7. Data showing safety, efficacy and convenience in use of the FDC has to be provided. If enough supportive literatures are not available, then 'adequate evidence' on its convenience to users has to be demonstrated.

8. In case of injectable formulation, sub-acute toxicity data conducted with the applicants' product has to be provided.

9. Source of bulk drugs /raw materials (for those ingredients which are considered new drugs) - If the applicant has a manufacturing license for bulk drugs, please provide a copy of the same. Otherwise, provide the consent letter from the approved source regarding supply of material.

Clarification: In case if the applicant does not have an approval from DCGI to manufacture any of the API which is considered as new drug, he can

- Import the API → Applicant has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents and comply with further requirements for import of API
- Manufacture the API → Applicant has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents and comply with further requirements for manufacture of API
- Obtain the API from another manufacturer which is not yet approved by DCGI → In such case the respective manufacturer of the API has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents. Such application will be processed simultaneously with the application for the FDC. Approval of the FDC will considered after approval of the API.

10. Copy of proposed Package Insert (generic name of all active ingredients; composition; dosage form/s, indications; dose and method of administration; use in special populations; contra-

indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions) and draft Label / Carton etc.

NOTE: No additional animal or human data are generally required

6.5 FDC - Subsequent approvals after the approval of primary applicant's FDC

CLARIFICATION:

FDCs which are of same strength/ratio, formulation and indication(s) of the already approved FDC of a primary applicant, the following documents are required to be submitted for subsequent approval of such FDCs for other applicants,

1. Form 44
2. Treasury Challan of INR 15,000 if all the active ingredients are approved in India for more than one year, or INR 50,000 in case any of the active ingredients is approved for less than one year.
3. Complete chemical and pharmaceutical data (As per Annexure I)
4. Regulatory status of the FDC including the details of various companies marketing the FDC
5. Bioavailability/Bioequivalence as required. When an FDC falling under Appendix VI(b)(i) of Schedule Y, is already approved in other country, for manufacture and marketing in India, applicant is required to submit chemical, pharmaceutical and clinical data generated abroad with the FDC. The guideline does not require conduct of BE study with the applicant's original formulation. Based on same principle, if an FDC is approved in India for first time, for subsequent approval applicant is required to submit chemical and pharmaceutical for the FDC. However, if any of the individual ingredients are approved for less than 4 years in India

and a BE study is required for the single ingredient formulation, a BE study is required to be conducted with the proposed FDC also).

6. In case of injectable formulation, sub-acute toxicity data conducted with the applicants' product has to be provided.
7. Source of bulk drugs /raw materials (for those ingredients which are considered new drugs) - If the applicant has a manufacturing license for bulk drugs, please provide a copy of the same. Otherwise, provide the consent letter from the approved source regarding supply of material.

Clarification: In case if the applicant does not have an approval from DCGI to manufacture any of the API which is considered as new drug, he can

- Import the API → Applicant has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents and comply with further requirements for import of API
- Manufacture the API → Applicant has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents and comply with further requirements for manufacture of API
- Obtain the API from another manufacturer which is not yet approved by DCGI → In such case the respective manufacturer of the API has to file separate application in Form-44 alongwith Treasury Challan of requisite fees and all relevant documents. Such application will be processed simultaneously with the application for the FDC. Approval of the FDC will considered after approval of the API.

8. Copy of proposed Package Insert (generic name of all active ingredients; composition; dosage form/s, indications; dose and method of administration; use in special populations; contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions) and draft Label / Carton etc.

7. ANNEXURES

7.1 ANNEXURE I

CHEMICAL AND PHARMACEUTICAL INFORMATION FOR MARKETING PERMISSION

Information on active ingredients:

Drug information (Generic Name, Chemical Name or INN) & Physicochemical Data including:

i. Chemical name and Structure - Empirical formula, Molecular weight
ii. Physical properties - Description, Solubility, Rotation, Partition coefficient, Dissociation constant
iii. Analytical Data: Elemental analysis, Mass spectrum, NMR spectra, IR spectra, UV spectra, Polymorphic identification
iv. Complete monograph specification including: Identification, Identity/quantification of impurities, Enantiomeric purity, Assay
v. Validations: Assay method, Impurity estimation method, Residual solvent/other volatile impurities (OVI) estimation method
vi. Stability Studies as per Appendix IX of Schedule Y (format of stability reports should be as per Annexure II): Final release specification, Reference standard characterization, Material safety data sheet.

Data on Formulation:

i. Dosage form
ii. Composition
iii. Master manufacturing formula
iv. Details of the formulation (including inactive ingredients)
v. In process quality control check
vi. Finished product specification & Method of Analysis
vii. Excipient compatibility study

viii. Validation of the analytical method

ix. Comparative evaluation with international brand(s) or approved Indian brands, if applicable

x. Pack presentation

xi. Dissolution

xii. Assay

xiii. Impurities

xiv. Content uniformity

xv. pH

xvi. Force degradation study

xvii. Stability evaluation in market intended pack at proposed storage conditions (format of stability reports should be as per Annexure II),

xviii. Packing specifications

xix. Process validation

7.2 ANNEXURE Ia

CHEMICAL AND PHARMACEUTICAL INFORMATION FOR CLINICAL TRIAL PERMISSION

Information on active ingredients:

Drug information (Generic Name, Chemical Name or INN) & Physicochemical Data including:

i. Chemical name and Structure - Empirical formula, Molecular weight
ii. Analytical Data: Elemental analysis, Mass spectrum, NMR spectra, IR spectra, UV spectra, Polymorphic identification
iii. Stability Studies: Data supporting stability in the intended container-closure system for the duration of the clinical trial.

Data on Formulation:

i. Dosage form,
ii. Composition,
iii. Master manufacturing formula,
iv. Details of the formulation (including inactive ingredients),
v. In process quality control check,
vi. Finished product specification & Method of Analysis,
vii. Excipient compatibility study,
viii. Validation of the analytical method.
ix. Stability Studies: Data supporting stability in the intended container-closure system for the duration of the clinical trial.

Note: 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.

7.3 ANNEXURE II

FORMAT FOR SUBMITTING THE RESULTS OF STABILITY STUDY OF NEW DRUGS

Stability testing: Summary sheet

Results of stability testing should be presented as shown below. A separate form should be completed for each pharmaceutical preparation tested:

Accelerated/real-time studies

Name of drug product

Manufacturer

Address

Active ingredient (INN)

Dosage form

Packaging

Batch Number	Date of manufacturing	Expiry date
1.		
2.		
3.		

Shelf-life

Batch Size Type of batch (experimental, pilot plant, production)

1.

2.

3.

Samples tested (per batch)

Storage/test conditions:

Temperature C Humidity %

Results:

1. Chemical findings

2. Microbiological and biological findings

3. Physical findings

4. Conclusions

Signature of competent / authorized personnel

Name:.....

Designation:.....

Date:.....

Note: Detailed stability study data / results in tabular form should also be enclosed along with the above summary sheet.