RTI Matter

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Government of India
Ministry of Health & Family Welfare
Department of Health & Family Welfare
****

Nirman Bhavan, New Delhi
Dated the 14th August, 2015

To,

Shri Prashant Reddy T, Advocate,
C/o Lex One Partners,
E-19, LGF,
Jungpura Extension,
New Delhi-110014.

Subject: RTI application of Shri Prashant Reddy T., Advocate-Regarding.

Sir,

On receipt of the requisite fee vide your letter dated 27.07.2015 (received on 11.08.2015 in this office from RTI Cell after removal of demand draft), the copies of the relevant documents (67 pages) are sent herewith.

Encl: As above

Yours faithfully,

(R.G. Singh)
Under Secretary (Drugs Quality Control) & CPIO
Telefax: 23063019

Copy to:

Ms. Sindhu Patil, Section Officer, RTI Cell, MoH&FW.

POLICY GUIDELINES FOR APPROVAL OF FIXED DOSE COMBINATIONS (FDCs) IN INDIA

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

CDSCO Central Drug Standards Control Organization

CPP Certificate of Pharmaceutical Product

CRF Case Record Form

CT Clinical Trial

DCGI Drugs Controller General (India)

D & C Drugs and Cosmetics

FDC Fixed Dose Combination

FDC-FPP Fixed Dose Combination Finished Pharmaceutical Product

FPP Finished Pharmaceutical Product

GCP Good Clinical Practice

GMP Good Manufacturing Practice

HIV Human Immunodeficiency Virus

ICF Informed Consent Form

IND Investigational New Drug

INN International Nonproprietary Names

INR Indian National Rupee

LD Lethal Dose

PK / PD Pharmacokinetic and Pharmacodynamic

SPC Summary of Product Characteristics

1.2 DEFINITIONS

Active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form that may be in the form of a salt, hydrate or other form of the active moiety, or may be the active moiety itself. Active moieties are intended to furnish effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Active moiety

The term used for the therapeutically active entity in the final formulation of therapeutic goods, irrespective of the form of the API. The *active* is alternative terminology with the same meaning. For example, if the API is propranolol hydrochloride, the active moiety (the active) is propranolol.

Applicant

The person or company who submits an application for marketing authorization of a new pharmaceutical product, an update to an existing marketing authorization or a variation to an existing market authorization.

Comparator

The finished pharmaceutical product with which the FDC-FPP is to be compared. The comparison may be by means of bioequivalence studies or clinical studies of safety and/or effectiveness. A single study may use more than one comparator, for example several single entity FPPs. A comparator may be a placebo.

Co-packaged product

A product consisting of two or more separate pharmaceutical products in their final dosage form that are packaged together for distribution to patients in the co-packaging.

Finished pharmaceutical product (FPP)

A product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more actives.

Fixed-dose combination (FDC)

A combination of two or more actives in a fixed ratio of doses. This term is used generically to mean a particular combination of actives irrespective of the formulation or brand. It may be administered as single entity products given concurrently or as a finished pharmaceutical product.

Fixed-dose combination finished pharmaceutical product (FDC-FPP)

A finished pharmaceutical product that contains two or more actives.

New chemical (or biological) entities

Actives that have not previously been authorized for marketing as a drug for use in humans in the country in question.

Reference product

A pharmaceutical product with which the new product is intended to be interchangeable in clinical practice. The reference product will normally be the innovator product for which efficacy, safety and quality have been established. Where the innovator product is not available, the product that is the market leader may be used as a reference product, provided that it has been authorized for marketing and its efficacy, safety and quality have been established and documented.

Summary of product characteristics (SPC)

A term used in the European Union. Product information or data sheets in the European Union should be based on the approved SPC.

2. BACKGROUND

The development of FDCs is becoming increasingly important from a public health perspective. The basic rationale of making "fixed dose combination" medicinal products is either to improve adherence or to benefit from the added effects of the two medicinal products given together. FDCs have shown to be particularly useful in the treatment of infectious diseases like HIV, malaria and tuberculosis where giving multiple antimicrobial agents is the norm. FDCs are also of use in chronic conditions especially when multiple disorders often co-exist.

FDCs are known to offer specific advantages over the single entity preparations, such as increased efficacy, and/or a reduced incidence of adverse effects, possibly reduced cost and simpler logistics of distribution relevant to situations of limited resources. Improved patient adherence and reduced development of resistance in certain cases of antimicrobial use are additional benefits.

FDCs must be based on convincing therapeutic rationalization and be carefully justified and clinically relevant. FDCs must be shown to be safe and effective for the claimed indications and it cannot be assumed that benefits of the FDC outweigh its risks. As for any new medicine, the risks and benefits must be defined and compared. Particular attention should be drawn to the doses of each active substance in the FDC

3. SCOPE

This document applies to the manufacture/ import and marketing approval of any FDC in the country.

4. GENERAL CONSIDERATIONS

The requirements for permission to manufacture/ import and market any FDC in the country are described below.

1. FDCs are classified into 4 broad categories and required data/ evidence for marketing approval/permission to conduct clinical trial/BA-BE studies is described under each category or sub-category thereof.

2. Co-packaged products will also be treated as FDCs .
3. A clear justification with a valid therapeutic rationale of the particular combination of active substances proposed along with the appropriate data as listed below will be the basis for approval as per Annexure 1.
4. It may not always be necessary to generate original data. Evidence may be obtained from the scientific literature, subject to its being of adequate quality as per Annexure 2.
5. The strategies and commitment of the applicant towards post marketing surveillance of the new FDC should be adequately addressed as per the Category of the FDC.
6. An application for a marketing authorization may comprise:
    a. Original data.
    b. Data from the literature.
    c. Both original data and data from the literature ("hybrid").

    For FDCs, it is likely that hybrid submissions will be the most common type.
7. Scientific literature rarely contains enough adequately validated information on the quality of the specific proposed FDC formulation (including Chemical and pharmaceutical data) to allow the full quality data set to be based solely on data from the literature. In particular, the complete formulation and method of manufacture are rarely specified in literature. Consequently the quality data set will almost always be totally original.
8. If the FDC is available in more than one strength or ratio of doses, each dose entity should be considered as a separate entity and there should be a risk–benefit assessment of each combination.
9. FDCs consisting of ONLY minerals, vitamins (as defined per Schedule V), or probiotics will be granted exemption from bioequivalence studies.
10. FDCs of veterinary products would not be in the purview of this guidance document.

5. DATA REQUIRED FOR PERMISSION TO MANUFACTURE/ IMPORT AND MARKET ANY FDC IN THE COUNTRY

The framework for issuing a marketing authorization for the FDC will be as per Schedule Y, 122-D; 122-DA , 122 E

5.1 Common Documents for all FDCs.

Following documents/ data must be submitted irrespective of the category

1. Form 44
2. Treasury Challan of INR 15,000 if all active pharmaceutical ingredients are approved in India for more than one year, or INR 50,000 in case any of the active pharmaceutical ingredients is approved for less than one year. The fee amount will be subject to change from time to time.
3. Rationale (As per Annexure 1) for combining the individual APIs of the FDC in the proposed ratio giving therapeutic justification along with supporting scientific data. (As per Annexure 2)
    a. If the actives in the FDC are intended to relieve different symptoms of a disease state, it is a prerequisite that these symptoms commonly occur simultaneously at a clinically relevant intensity and for a period of time such that simultaneous treatment is appropriate. Occurrence of the individual symptom in isolation should not be indications for the FDC.
4. For those ingredients which are approved and considered new drugs, give source of bulk drugs /raw materials.
    a. If the applicant has a manufacturing license for bulk drugs, please provide a copy of the same.
    b. Otherwise, provide the consent letter from the approved source regarding supply of material.
5. In case the applicant does not have an approval from DCGI to manufacture any of the Active Pharmaceutical Ingredients (API) in the country then it is considered a new drug and the applicant can

a. *Import the API*

Applicant has to file a separate application in Form-44 along with treasury challan and all relevant documents and comply with further requirements for import of API

b. *Manufacture the API*

Applicant has to file separate application in Form-44 along with treasury challan and all relevant documents and comply with further requirements for manufacture of API

c. *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 manufacture of API.

6. The regulatory status of the formulations of the individual APIs of the FDC in other countries (if relevant).

- Country of Origin
- Countries where the formulations of the individual APIs of the FDC is
  - Approved
  - Marketed
  - Withdrawn, , with reasons
- Restrictions on use, if any, in countries where marketed/ approved
- Free sale certificate (FSC)/ certificate of pharmaceutical product (COPP) from the country of origin (in case of import of the finished form of the individual drugs of the FDC).

7. The regulatory status of the FDC in other countries (if relevant).
    - Country of Origin
    - Countries where the FDC is
        - Approved
        - Marketed
        - Withdrawn, , with reasons
    - Restrictions on use, if any, in countries where marketed/ approved
    - Free sale certificate (FSC) / certificate of pharmaceutical product (COPP) from the country of origin (in case of import of the finished form of the FDC).

    Note: Clearly mention the names of the countries where the FDC is approved/ marketed or withdrawn.
8. Complete chemical and pharmaceutical data including stability data (As per Annexure 3)
9. GMP certification of sites of manufacture
10. Strategies for Post-marketing surveillance (As per Annexure 4)
11. Proposed specifications and Certificate of analysis of study drug(s)
12. Copy of package inserts and promotional literature of FDC if marketed abroad.
13. Copy of proposed Package Insert containing
    a. Generic name of all active ingredients;
    b. Composition;
    c. Dosage form/s,
    d. Indications;
    e. Dose and method of administration;
    f. Use in special populations;
    g. Contra-indications; Warnings; Precautions;
    h. Drug interactions;
    i. Undesirable effects;
    j. Overdose;
    k. Pharmacodynamic and pharmacokinetic properties;
    l. Incompatibilities;
    m. Shelf-life;
    n. Packaging information;
    o. Storage and handling instructions and
    p. Draft label / carton etc.

5.2 Categories of FDCs and data required for manufacture/ import and marketing approval of these Categories

5.2.1 Category I

One or more active pharmaceutical ingredient(s) of the FDC is a new drug (as per Rule 122E of D&C Rules, 1945) not approved in India.

For such FDCs to be approved for manufacture/ import and marketing, the data required to be submitted will be the same as that for a new chemical entity (NCE) as per Schedule Y

Notes

1. Data and documents required for permission to conduct clinical trials are described in Annexure 5.

EXCEPTION I

A. If the individual APIs of the FDC and the proposed FDC is already marketed in another country (not in India) with regulatory systems comparable to the Indian regulatory system

OR

B. If the FDC is already marketed in India, however, one of the APIs is not approved as proposed in the new FDC e.g. new indication or dosage.

OR

C. If the FDC is already marketed in India, however, a change of ratio of the active ingredients in the FDC is sought, and one of the APIs is not approved in the strength proposed

THEN

i. All non-clinical and clinical data must be submitted along with any other literature (as per Annexure 2)

ii. An application will be considered for waiver of Phase I and II studies based on submitted data.

iii. Phase III studies will need to be conducted as per Annexure 6.

5.2.2 Category II

All active pharmaceutical ingredients are approved/ marketed in India individually and the FDC is proposed for marketing

These are further classified into the following:

Category IIA

A similar FDC is marketed in another country with a regulatory system similar to India, for the same indication

This group of FDCs includes those in which active pharmaceutical ingredients already approved/ marketed individually are combined for the first time, for a particular therapeutic claim but, are being marketed abroad as FDC with an established safety and efficacy in humans.

For marketing approval of such FDCs, following documents/ data (in addition to the common documents) have to be submitted:

1. Report [as per Annexure 7 (section 7.2)] of Bio-equivalence study conducted as per Annexure 7 proving the FDC & the active APIs given concurrently are bioequivalent. [Bio-waiver may be granted in cases as described in Annexure 7]

2. Literature (as per Annexure 2) pertaining to

a. Drug-Drug-Interactions (known and/or expected) among the active pharmaceutical ingredients present in the FDC, along with its implications.

b. Clinical trials data (conducted as per good clinical practices) showing safety and efficacy of the FDC in the same strength (that has been carried out in other countries) including published data.

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

Category IIB

FDC Not marketed anywhere but individual APIs used concomitantly for the same indication, at the same dose

For approval of such FDCs, following documents (in addition to the common documents) have to be submitted,

1. Report [as per Annexure 7 (section 7.2)] of Bio-equivalence study conducted as per Annexure 7 proving the FDC & the active APIs given concurrently are bioequivalent. [Bio-waiver may be granted in cases as described in Annexure 7]
2. Literature (As per Annexure 2) pertaining to

a. Drug-Drug-Interactions (known and/or expected) among the active pharmaceutical ingredients present in the FDC, along with its implications.

b. Available pharmacological, toxicological and clinical data on the individual ingredients

c. Clinical data showing safety and efficacy of the concurrent use of the individual active ingredients in the same indication in the same strength (that may have been carried out in other countries) including published data. Available data of clinical trials should be provided.

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

5.2.3 Category III

FDC - Marketed in India but some changes are sought

These are further classified as:

Category IIIA

Change in the ratio of active pharmaceutical ingredients (provided single entity doses are approved) and the doses of the individual components are within the approved dose range for the individual drugs

For manufacture/import and marketing permission the following data in addition to the common documents

1. Literature (As per Annexure 2) pertaining to
a. Clinical data showing safety and efficacy of the FDC / Concomitant use of the ingredients, in the strength in which it is proposed to be marketed
b. Summary of Drug-Drug-Interactions (known and/or expected) among the active pharmaceutical ingredients present in the FDC, at the proposed doses along with its implications.
2. *In vitro* studies (As per section 3.2.1 "In vitro studies" of CDSCO guidelines for BA/BE)
3. In case of injectable formulation, acute as well as sub-acute toxicity data conducted with the applicants' product has to be provided.

Category IIIB

Make a new dosage form and/or a new route of administration for the same indication (provided the new dosage form and/or route of administration are approved for the single entity)

For manufacture/import and marketing permission the following data in addition to the common documents

1. Report [as per Annexure 7 (section 7.2)] of Bio-equivalence study conducted as per Annexure 7 proving the FDC & the active APIs given concurrently are bioequivalent. [Bio-waiver may be granted in cases as described in Annexure 7]
2. Literature (As per Annexure 2) pertaining to

a. Drug-Drug-Interactions (known and/or expected) among the active pharmaceutical ingredients present in the FDC, along with its implications.
b. Available pharmacological, toxicological and clinical data on the individual ingredients

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

5.2.4 Category IV

Subsequent approvals after the approval of primary applicant's FDC

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

1. Regulatory status of the FDC including the details of various companies marketing the FDC
2. Complete chemical and pharmaceutical data including stability data (as per Annexure 3) for the proposed FDC.
3. Report [as per Annexure 7 (section 7.2)] of Bio-equivalence study conducted as per Annexure 7 proving the FDC & the active APIs given concurrently are bioequivalent. [Bio-waiver may be granted in cases as described in Annexure 7]

Annexure 1

Rationale for Fixed Dose Combination

1. For granting manufacturing/marketing approval of a new FDC, it will have to be shown that it is rational to combine two or more APIs into a single product. An application should clearly state in the section on rationality:
   - Basis of making the claim for the FDC (see point 2 below)
   - Proposed dosing schedule with scientific evidence (if available) for the combination
   - Potential for clinically significant PK and/or PD interactions between the APIs proposed to be combined, leading to safety concerns.
   - Existing recommendations on specific safety issues (e.g .concerns in special populations, need for a QTc study, etc.)
2. Rationality will depend on medical, quality and bioavailability considerations.

1. **Quality:** The same quality standards that apply to single-component products will apply to FDCs. It will be necessary to demonstrate that the quality of the combination is similar to that of the individual ingredients.

2. **Medical:**

   i. There should be a medical rationale for combining the actives.

   ii. If the actives in an FDC are intended to relieve different symptoms of a disease state, it is a prerequisite that these symptoms commonly occur simultaneously at a clinically relevant intensity and for a period of time such that simultaneous treatment is appropriate. Occurrence of the individual symptom in isolation should not be indications for the FDC.

   iii. The FDC should have demonstrably one or more of the following features:

      a. Increased efficacy in comparison to the individual components given at the same dose,

b. The incidence of adverse reactions in response to treatment with the combination is lower than in that in response to any of the component actives given alone, for example as a result of a lower dose of one component or a protective effect of one component.

c. Dose reduction

d. Reduced cost

e. One drug acts as a booster for another (for example in the case of some antiviral drugs).

f. Improved adherence, simplified therapy,

g. For antimicrobials, the combination results in a reduced incidence of resistance.

h. Minimize abuse of other actives

i. Simplified logistics of procurement and distribution.

iv. There should be an identifiable patient group for which this combination of actives and doses are indicated. The larger the patient group in question, the more significant is this factor.

v. In general, the actives in a combination should have similar pharmacokinetics. If this is not the case, the applicant should explain and justify the combination.

vi. In general, all of the actives in a combination should have a similar duration of action. If this is not the case, the applicant should explain and justify the combination.

vii. Dose and proportion of each active ingredient present is appropriate for the intended use

viii. Several dose combinations for each substance might have to be tested and the concentration-response information can help to select the fixed combinations leading to satisfactory response

ix. If there is an increase in the number or severity of adverse reactions to the FDC as compared with those in response to the individual actives given alone, evidence and argument should be presented showing that the advantages of the combination outweigh the disadvantages. These should be included in the section of the submission entitled "Balancing the advantages and disadvantages of a new FDC".

3. **Interpretation of the results of bioavailability (BA) and bioequivalence (BE) tests** involves both quality and medical considerations. For example, it is not acceptable that bioavailability of the FDC is reduced or variable, when compared with that of single entity products, because of poor formulation, but an interaction between two actives that leads to an increased bioavailability may be one of the advantages that is taken into account when balancing advantages and disadvantages.

In addition to the above, any disadvantages that the FDC is likely to have [for example as listed (not be restricted to) below] must also be listed with the rationality description in the application.

Possible disadvantages of a new FDC

1. Either the doses of the components, and/or the ratio of doses, typically differ from patient to patient
2. Patients are likely to be taking different doses at different stages of treatment (for example initial treatment compared with long-term treatment)
3. These two factors are particularly significant when one or more of the actives has a narrow therapeutic index and/or a steep dose–response curve in the therapeutic range
4. There is a higher incidence or greater severity of adverse reactions to the combination than with any of the ingredients given alone, or there are adverse reactions not seen in response to treatment with any of the individual ingredients.

5. There are unfavorable pharmacokinetic interactions between the ingredients, for example when one drug alters the absorption, distribution, metabolism or excretion of another.
6. Dose adjustment is necessary in special populations, such as in people with renal or hepatic impairment, or the elderly.
7. The product (tablets or capsules), is so large that patients find it difficult to swallow

Annexure 2

Principles for Determining whether Data from Scientific Literature are Acceptable

Literature-based data concerning FDCs will be acceptable, subject to the principles below.

1. **Original study reports are preferred always.**
2. Only in their absence will published literature be considered if it meets the below criteria
   i. The overall strength of literature-based evidence will depend on its **quality, quantity and consistency of outcomes**.
   ii. All documents that are **directly relevant** to the application with respect to claim of FDC should be submitted.
   iii. Literature-based submissions **should** include:
      a. Separate sections for clinical, non-clinical and quality data
      b. Details of the search strategy, including a list of the databases searched and the service provider.
      c. The dates on which the search was performed (in order to establish that the search is adequately recent).
      d. The rationale for the search strategy, including an explanation of and reasons for the inclusion and exclusion criteria of the retrieved literature.
      e. An unedited search strategy and the outcome thereof.
      f. Cross-references to appended copies of publications and to any original data submitted.
      g. Appraisal of the sources of information, in particular whether the data comes from an independently refereed source or from other sources.
      h. An analysis (see point iv) of the data collected, including both favourable and unfavourable results; **this is a critical component of a submission that includes data from the scientific literature.**
      i. Searches should preferably be stratified according to patient groups such as age and ethnicity.

iv. The applicant's analysis of literature-based data should include an appraisal of:

a. The level of evidence of the data.

b. Relevance to the application being made (including a comparison of formulations and methods of manufacture of products used in clinical studies reported in the literature with those proposed for marketing).

c. Consistency and compatibility of the data from the literature with any original data submitted.

d. The impact of the literature-based data on the risk–benefit assessment for the FDC.

e. Any contradictions between favorable and unfavorable results.

v. If at the time of submission, a **literature search and/or the analysis of data from the literature** is more than 1 year old, the submission should justify using this search and analysis and should indicate why more recent publications and data have not been used. Alternatively a supplementary review of the more recent literature may be appended to the report that brings it to within 1 year of the date of submission.

vi. Copies of all documents referred to in the submission or in the data analysis should be appended to the submission. If a document is not in the English language, a certified translation should also be attached (in addition to the original).

vii. The following type of articles are acceptable in principle

a. Review articles published in reputed peer reviewed journals

b. Searches of company or in-house databases (including post-marketing surveillance reports): however it shall be clearly identified as in-house data

viii. The relative strength of clinical publications will generally be in the following order:

a. Meta-analyses/ Systematic Reviews.

b. Randomized controlled clinical trials.

c. Cohort/case–control studies.

d. Uncontrolled studies.

e. Case descriptions.

ix. Clinical studies published according to accepted reporting guidelines (for example CONSORT, Cochrane and others) will generally be preferred over studies that fail to report all pertinent data (e.g. safety data).

x. Publications from peer-reviewed journals will be preferred. .

xi. Clinical study reports which meet current standards of design and control, including compliance with a code of good clinical practice will carry more weight.

xii. Reports of non-clinical studies will be preferred that:

a. Include individual animal reports.

b. Are reported according to Schedule Y.

c. Are in compliance with the principles of Good Laboratory Practice (GLP).

Annexure 3

3.1 Chemical and Pharmaceutical Information for Marketing Permission and Stability Study Data

1. **Information on active pharmaceutical ingredients:**
    a. 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 Section 3.3 below). Final release specification, Reference standard characterization, Material safety data sheet.
        vii. The relationship of polymorphic and isomeric form of API on its activity shall be clearly elaborated.

2. **Data on Formulation:**
    a. Dosage form
    b. Composition
    c. Master manufacturing formula
    d. Details of the formulation (including inactive ingredients)
    e. In process quality control check
    f. Finished product specification & Method of Analysis

g. Excipient compatibility study
h. Process validation
i. Validation of the analytical method
j. Comparative evaluation with international brand(s) or approved Indian brands, if applicable
k. Pack presentation
l. Dissolution
m. Assay
n. Impurities
o. Content uniformity
p. pH
q. Stability evaluation in market intended pack at proposed storage conditions (format of stability reports should be as per Annexure II),
r. Packing specifications
s. The details of site of manufacture and permission for the same.

3.2 Chemical and Pharmaceutical Information for Clinical Trial Permission

1. Information on active ingredients

a. Drug information (Generic Name, Chemical Name or INN) & Physicochemical data including:

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

2. Data on Formulation:

a. Dosage form,
b. Composition,

c. Master manufacturing formula,

d. Details of the formulation (including inactive ingredients),

e. In process quality control check,

f. Finished product specification & Method of Analysis,

g. Excipient compatibility study,

h. Validation of the analytical method.

i. Stability Studies: Data supporting stability in the intended container-closure system for the duration of the clinical trial.

j. The details of site and permission where the proposed product is manufactured for the purpose of 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.

3.3 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.

Annexure 4

Pharmacovigilance for FDCs

This will be applicable for safety monitoring of the FDCs. Pharmacovigilance of the FDCs will operate under the aegis of PvPI (Pharmacovigilance Programme of India) 2010. It needs to be done throughout the life cycle of the product.

1. Sponsors will have to submit a detailed pharmacovigilance plan along with marketing authorization application.
2. Pharmacovigilance plan should mention
    a. Safety data from clinical development
    b. All the potential risks of an FDC
    c. Summary of anticipated risks
    d. Population at risk and
    e. Situations not adequately studied
    f. All the potential drug - drug and drug – food interactions of the FDC either as a separate document with pharmacovigilance plan or pharmacovigilance strategies or in the section referring to safety specifications of the Common Technical Document (CTD)
3. For FDCs of antimicrobials, monitoring of patterns of resistance will be an important component of pharmacovigilance. Hence, strategies for monitoring and prevention of the resistance should be mentioned in a separate section of the CTD.
4. Except for category IV (where passive surveillance would be sufficient) all the categories will have to undergo active surveillance.
5. If any significant safety concerns arise during clinical trials which warrant studies in special populations such as children, elderly, pregnant women or in hepatic or renal failure

patients, the protocol of such studies should be submitted along with the pharmacovigilance plan.

6. Protocols for comparative observational studies (cross sectional/ case control/ cohort), drug utilization study or any targeted clinical evaluation to be conducted as a part of pharmacovigilance plan need to be submitted along with the marketing application.

7. All phase IV protocols for new drugs (till four years after approval) will have to receive clearance from licensing authority as well as duly registered Institutional Ethics Committees (IECs).

8. Whenever a signal is generated for an individual component of an FDC or one of the components gets withdrawn anywhere from the world market, then the signal should also be generated for the particular FDC. The decision to withdraw the FDC will be taken after assessment of the risks and benefits *vis à vis* the proposed rationale.

9. For an FDC of antimicrobial agents, a signal will be generated if there is an alarming rise in the incidence of resistance to a particular FDC for the particular claim proposed.

Annexure 5

Data Required for Permission to Conduct Clinical Trials

Data required for permission to conduct clinical trials will be as follows:

5.1 Data Common to All phases of Clinical Trial

The following forms/data will be submitted with all applications for permission to coduct clinical trials irrespective of the phase of drug development

1. Form 44
2. Treasury Challan of INR 50,000 (for Phase- I) / 25,000/- (for Phase-II/III clinical trials).
3. Application in Form -12 along with T-Challan of requisite fees (in case of import of investigational products)
4. Regulatory status in other countries

   A. Countries where the drug is

      i. Approved

      ii. Marketed

      iii. Withdrawn, if any, with reasons

   B. Restrictions on use, if any, in countries where marketed/approved
5. Source of bulk drugs /raw materials.

Clarification:

Import the API

Applicant can import small quantity of the API under Form-11 for which separate application in Form-12 along with Treasury Challan and all relevant documents should be submitted.

Manufacture the API

Applicant can manufacture small quantities under license in Form-29 obtained from State Licensing Authority.

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 seeking NOC to manufacture small quantities for clinical trial purpose. Based on NOC from CDSCO license in Form-29 is required to be obtained from the concerned State Licensing Authority before manufacturing the trial batches.

6. Chemical and pharmaceutical information as per Annexure 3(Section 3.2)
7. Reports of any other clinical studies conducted with the proposed FDC.

5.2 Data/ Documents required according to the Phase of Study

The data required according to the phase of the clinical trial is as follows:

I. **Phase I Clinical Trials**

1. Animal Pharmacology

a. Summary
b. Specific pharmacological actions
c. General pharmacological actions
d. Follow-up and Supplemental Safety Pharmacology Studies
e. Pharmacokinetics: absorption, distribution; metabolism; excretion

2. Animal Toxicology

a. General Aspects
b. Systemic Toxicity Studies
    i. Single dose toxicity studies
    ii. Dose Ranging Studies
    iii. Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure. (As per Clause1.8 of Appendix-III of Schedule Y to Drugs & Cosmetics Rules.)

c. Male Fertility Study
d. Segment I [female fertility] Female Reproduction and Developmental Toxicity Studies

e. Local toxicity with proposed route of clinical application (duration depending on proposed length of clinical exposure)

f. Allergenicity/Hypersensitivity (when there is a cause for concern or for parenteral drugs, including dermal application)

g. Photo-allergy or dermal photo-toxicity test (if the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential)

h. *In vitro* Genotoxicity

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 1945 respectively. Depending upon the nature of new drugs and disease(s) specific additions/deletions may be made to the said requirements.

3. **The Proposed Protocol for Conducting The Clinical Trial**

4. **Investigator's Brochure**

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

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

7. **Registration number of Ethics Committee/s that will oversee the trial**

8. **Case Record Form (CRF)**

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

10. **Undertaking by Sponsor(s)**

II. Phase II Clinical Trials

1. Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I trial, with appropriate references.

2. In case of an application for directly starting a Phase II trial - complete details of the nonclinical safety data needed similar to that needed for obtaining the permission for conduct of Phase I trial, as per the list provided above must be submitted.

3. Results of Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure

4. *In-vivo* genotoxicity tests

5. Segment II female reproductive/developmental toxicity study (if female patients of child bearing age are going to be involved)
6. Clinical study report of Phase I study/studies
7. The Proposed protocol for conducting the clinical trial
8. Investigator's Brochure
9. Patient Information Sheet and Informed Consent Form (ICF) as per Appendix V and Appendix XII of Schedule Y
10. Copy of 'Ethics Committee' approval letters (if available)
11. Registration number of Ethics Committee/s that will oversee the trial
12. Case Record Form (CRF)
13. Undertaking by Investigator(s) as per Appendix VII of Schedule Y and CV
14. Undertaking by Sponsor(s)

III. <u>Phase III Clinical Trials</u>

1. Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I and II trials, with appropriate references.
2. In case of an application for directly initiating a Phase III trial - complete details of the non-clinical safety data needed for obtaining the permissions for Phase I and II trials, as per the list mentioned above must be provided.
3. Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure (As per Schedule Y)
4. Reproductive/developmental toxicity studies
5. Segment I (if female patients of child bearing age are going to be involved), and Segment III (for drugs to be given to pregnant or nursing mothers or where there are indications of possible adverse effects on foetal development)
6. Carcinogenicity studies (when there is a cause for concern or when the drug is to be used for more than 6 months).
7. Clinical study report of Phase I study/studies
8. Clinical study report of Phase II study/studies

9. The Proposed protocol for conducting the clinical trial

10. Investigator's Brochure

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

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

13. Registration number of Ethics Committee that will oversee the trial

14. Case Record Form (CRF)

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

16. Undertaking by Sponsor(s)

17. Prescribing information (of the drug circulated in other countries, if any)

IV. Phase IV Clinical Trials (Please see Annexure 4)

Note: Licensing authority approval will be required, when the drug is still a 'new drug' as per Rule 122E of D & C Rules, 1945.

1. Drug approval details including conditions for marketing. The Proposed protocol for conducting the clinical trial Investigator's Brochure

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

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

4. Registration number of Ethics Committee that will oversee the trial

5. Case Record Form (CRF)

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

7. Prescribing information.

8. Post Marketing Surveillance data of the FDC.

9. Clinical data generated post grant of marketing authorisation.

Annexure 6

Conducting Clinical Trials (Phase III)

The clinical studies should fulfill the following conditions:

i. Clinical studies should be designed to determine whether the combination has an advantage over the individual active components given alone.

ii. The study should be conducted in appropriate patient population with an adequate sample size to give the study 80% power and an alpha error of 5%.

iii. The studies should be planned so that there is regional representation to all populations in the country (sites should be selected from the east, west, centre, north, south of India).

iv. The sites should be approved by the DCGI,

v. Sites should have Institutional Ethics Committees registered with the CDSCO.

vi. The data should preferably demonstrate that each active contributes to the therapeutic effect of the combination.

It may not be possible to show that all of the components have efficacy when administered as single entities; for example, clavulanic acid has little or no antimicrobial activity when given alone, but it enhances the efficacy of beta-lactam antibiotics.

vii. The choice of comparators for the purpose of safety and efficacy studies

   a. Should be justified.
   b. They should normally represent the recognized treatment for the indication in question.
   c. Comparators should preferably be licensed products with well-established safety and efficacy profiles and of established quality.
   d. Unapproved or novel combinations should be avoided as comparators as they may introduce new efficacy or toxicity characteristics and thus complicate assessment of the combination under test.

viii. The FDC should be shown, directly or indirectly, to be superior to the component actives given as single entity treatments. **Only a superiority trial can give the necessary**