DRAFT POLICY FOR APPROVAL OF FIXED DOSE COMBINATIONS (FDCs)

CENTRAL DRUGS STANDARD CONTROL ORGANIZATION

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MINISTRY OF HEALTH & FAMILY WELFARE

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Contents

ABBREVIATIONS

API Active Pharmaceutical Ingredient

BA Bio-availability

BE Bio-equivalence

CDSCO Central Drug Standards Control Organization

CT Clinical Trial

DCGI Drugs Controller General (India)

D & C Drugs and Cosmetics

ND&CT Rules, 2019 New Drugs and Clinical Trial Rules, 2019

FDC Fixed Dose Combination

GCP Good Clinical Practice

GMP Good Manufacturing Practice

ICF Informed Consent Form

IND Investigational New Drug

INN International Nonproprietary Names

INR Indian National Rupee

PK / PD Pharmacokinetic and Pharmacodynamic

1. 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. However, irrational FDCs can pose serious risk to the patients. Considering these aspects, it is very important to address this public health issue by developing a policy documents for the approval of FDCs in the country.

2. POLICY FOR APPROVAL OF FDCS:

As a matter of policy, FDCs are mainly approved in the country fulfilling following criteria:

- FDCs have shown to be particularly useful in the treatment of infectious diseases like HIV, malaria and tuberculosis where giving multiple antimicrobialagents 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. 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 inthe country. This document is not applicable for Veterinary products.

4. VARIOUS SCENARIOS

The detailed requirements with respect to approval of FDCs have been published under New Drugs and Clinical Trial Rules, 2019. Considering these requirements, manufacture/ import

and marketing approval of any FDC will fall into any one of the following scenarios:

1. One or more of the ingredients of the combination is a New Drug not approved
2. 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
3. FDC Marketed in other Country (FDC Marketed Abroad)
4. Not Marketed anywhere but individual components used concomitantly
5. Not marketed anywhere and individual component are not used concomitantly
6. FDC already approved in the country (Subsequent Applications)
7. Marketed in India But Some Changes are Sought
    a. New Dosage Form
    b. New route of administration
    c. New Indication
    d. Additional Strength
    e. Modified release dosage form
8. Only for Convenience

5. POLICY CONSIDERATIONS WHILE APPROVING ANY FDCs

5.1 Medical Rationale:

1. 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 assessmentof each combination.
2. For granting 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:
    i. Basis of making the claim for the FDC
    ii. Proposed dosing schedule with scientific evidence (if available) for the combination
    iii. Potential for clinically significant PK and/or PD interactions between the APIs proposed to be combined, leading to safety concerns.
    iv. Existing recommendations on specific safety issues (e.g .concerns in special populations, need for a QTc study, etc.)

3. Medical Consideration:

i. 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.

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

a. Increased efficacy in comparison to the individual componentsgiven 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. One drug acts as a booster for another (for example in the case of some antiviral drugs).

e. Improved adherence, simplified therapy,

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

g. Minimize abuse of other actives

iii. 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 moresignificant is this factor.

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

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

5.2 Principles for Determining Whether Clinical Data from Scientific Literature are Acceptable

i. The analysis of published literature-based data should include an appraisal of:

a. The level of evidence of the data.

b. Relevance to the application being made.
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.
e. Any contradictions between favorable and unfavorable results.

ii. 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.

iii. The relative strength of clinical publications should 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.

5.3 Data Requirement

The detailed requirements have been prescribed under Second Schedule of the ND&CT Rules, 2019 which can be referred for the purpose.

5.4 Conduct Of Bioavailability (BA)/Bioequivalence (BE) Studies

A. General

i. For approval of new FDCs, it is important to determine that the rate and extent of absorption of each therapeutic moiety in an FDC product are the same as the rate and extent of absorption of each therapeutic moiety administered concurrently as separate single-ingredient products. For approval of FDCs for which reference products exist, applicants should show that the rate and extent of absorption of each component of the FDC are the same as those of each component of approved FDC in the country. This evaluation provides the link between the new combination drug product and the drug product(s) whose safety, efficacy, and quality parameters are well established.

ii. The CDSCO Guidelines for Bioavailability and Bioequivalence Studies, 2005 (available at www.cdsco.nic.in) should be referred for design and conduct of all studies

iii. If it is known with certainty (e.g. from published data) that the any one of the products is

affected by food, then a BA/BE study in fed state is recommended.

B. Choice of the comparator

i. For a Subsequent FDC where the FDC is already approved, it should be compared to the brand that was first marketed in India for which safety and efficacy is established. If more than one similar FDCis available, and the choice of comparator may not the first marketed FDC, any approved FDC may be considered as the comparator for the proposed BE Study design.

ii. For an FDC was approved in other country the comparator should be the FDC that is marketed abroad.

iii. For an FDC is not approved, single entity products should be the comparator and should be given concurrently will be used in the proposed BE Study.

C. Conditions When Bio-Waivers Can Be Granted

Biowaiver are granted as per CDSCO Guidelines for Bioavailability and Bioequivalence Studies, 2005 (available at www.cdsco.nic.in) – where all conditions are met by all the components of the FDC.

5.5 Pharmacokinetic Studies

a. In general, it is desirable that there should be no pharmacokinetic or pharmacodynamic interactions between the components of a FDC.

b. However, there are circumstances in which such an interaction is intentional and may even contribute to the therapeutic outcome. For example:

   i. Ritonavir boosts the activity of protease inhibitors.

   ii. Carbidopa and benserazide both reduce decarboxylation of levodopa in the gut wall, and consequently reduce the dose of levodopa that should be administered.

   iii. Clavulanic acid reduces bacterial hydrolysis of beta lactam antibiotics and consequently both increases the concentration and prolongs the duration of effectiveness.

c. Tests should be conducted to elucidate any pharmacokinetic or pharmacodynamic interaction between the actives in a combination. Any interaction should be quantified so that its effect on safety and efficacy is eitherpredictable or (preferably) has been tested in a clinical study. Interactions may be additive,synergistic or antagonistic.

d. If there is an unintended pharmacokinetic interaction between the actives, it should be demonstrated that the therapeutic advantages of the combination outweigh any disadvantages

resulting from the interaction.

5.6 Clinical Trials Consideration:

The clinical studies should fulfill the following conditions:

i. The study should be conducted in appropriate patient population with an adequate sample size to give the study minimum of 80% power and an alpha error of 5% (0.05).

ii. The data should preferably demonstrate that each active ingredient in the FDC contributes to the therapeuticeffect of the combination. It may not be possible to show that all the components have efficacy when administeredas single entities; for example, clavulanic acid has little or no antimicrobial activity when given alone, but it enhances the efficacy of beta-lactam antibiotics.

iii. 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 statistical confidence. However, non-inferiority design may be considered where relevant (given adequate and scientific/ethical justification).**

iv. Depending on the claim, superiority or non-inferiority should be demonstrated for each specified clinical outcome. For example, if the claim for the FDC is "less bone marrow depression", and similar efficacy as compared to the one or more of the actives, a non-inferiority outcome should be demonstrated for efficacy and a superiority outcome for safety.

v. In clinical trials that are intended to test for superiority and/or non-inferiority, the choice of comparator should be carefully considered and will depend in part on the medical and ethical circumstances. The comparator may be:

    a. The treatment whose risk–benefit profile is best supported by evidence or is atleast well established.
    b. One or more of the actives in the FDC given as a single treatment.
    c. A placebo (where scientifically needed and ethically justified).

vi. If the combination is intended for long-term use, data on safety in patients will normally be required for 6 months or longer for e.g., Cardiovascular drugs, Anti diabetic drugs etc.

vii. End-points in clinical trials should be such as to characterize the advantages and

disadvantages of the combination. For example, for a combination designed to reduce the development of drug resistance, end-points might include the frequency of new drug resistance as well as the overall clinical outcome.

Multi factorial designs and parallel group comparisons are useful means by which it maybe possible to demonstrate that a combination is superior to the individual actives

5.7 Co-Packaged Products

a. Co-packaged product consists of two or more separate pharmaceutical products in their final dosage forms that are packaged together for distribution to patients in the co-packaging.
b. Co-packaged products may fall into any of various scenarios under S.No 4.
c. A full quality data set is required for all components of Co-packaged pharmaceutical products, except for any component that already has marketing authorization in which case more limited requirements apply.
d. If one or more of the pharmaceutical products already has marketing authorization, then the additional quality information to support co-packaging of those pharmaceutical products should be limited to data on stability of the products in the co-packaging. However the manufacturer of each component pharmaceutical product should provide an assurance that the product as used in co-packaging will be identical in formulation and method of manufacture to the one that already has marketing authorization. This is especially important when the manufacturer of a component is not the manufacturer of the co-packaged product.
