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Review Article

REGULATORY REQUIREMENTS AND REGISTRATION PROCESS FOR DRUG APPROVAL OF FIXED DOSE COMBINATIONS (FDCs) IN INDIA: A REVIEW

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ABSTRACT

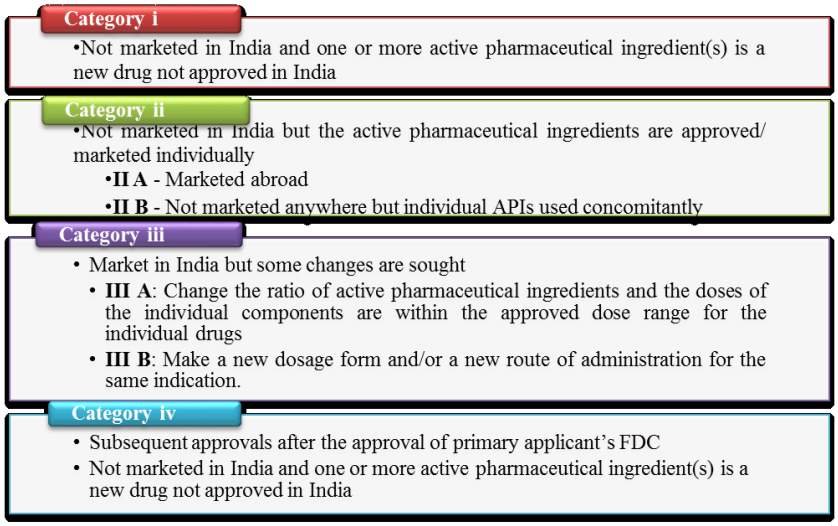
The article reveals the data required for fixed-dose combinations (FDCs) in Indian market occupies a higher pedestal when the efficacy of a finished product is under question. Although these have advantages that make them appear a good therapy option, In the Indian market, FDCs occupies a huge share; therefore the rational approval of FDCs is important for the development of public health perspectives in India. Some of the data required for market authorization balancing of advantages, disadvantages and Pharmacovigilance. Bioavailability (BA)/Bioequivalence (BE) studies are the basis for regulatory considerations of FDC product discussed according to India. Therefore, before getting an FDC approval, a manufacturer has to make available information to the health authority on quality, safety, efficacy and post-marketing surveillance studies (PMS). we shall briefly see the data required to be made available to the Central Drug Standard Control Organization (as per relevant guidelines) to get an FDC approved and the registration process.

Keywords: Fixed Dose Combinations (FDCs), CDSCO, Market authorization, Registration, Regulations, post-marketing surveillance

INTRODUCTION

Fixed-dose combination drugs (FDCs) are formulations that contain two or more active ingredients in a single dose.[1] More than one medication is as often as possible used for treatment of either single disease or multiple disease conditions. The FDCs formulation may have up to five or even more drug ingredients with or without rationality of their presence and in the quantity.[2]These medicines are formulated to have a similar bioequivalence of the two different drugs as separate medicine and therefore have similar pharmacokinetics and pharmacodynamic effects, as well as reducing the dose- related side effects of a single drug. FDCS were useful in the treatment of diseases like hypertension, diabetes, pain, HIV, malaria, tuberculosis, depression, asthma and chronic obstructive pulmonary disease (COPD).FDCs are classified into four types according to their regulatory status.[3] Appendix VI of Schedule Y (Drugs & Cosmetics act 1940 and Rules 1945) in India states the requirements for marketing approval of all types of FDCs.[4]

CLASSIFICATION OF FDCs



ADVANTAGES OF FDCs

- Lower doses and fewer side effects
- Early treatment targets
- Better compliance
- Lower administrative cost
- Target infectious agents rather than body tissue
- Combination of products lines as well as therapies
- Patent extension

DISADVANTAGES OF FDCs

- Pharmacokinetics mismatch and having peak efficacy at different time
- Chemical incompatibility leading to decreased shelf life
- Its therapeutic efficacy has not been proved scientifically
- Drug interactions because of the common metabolizing pathways
- The product (tablets or capsules) is so large that patients find it difficult to swallow

RATIONALE FOR FDCs

Quality
A similar quality benchmarks that apply to single drug-products will apply to FDCs. It will be important to show that the quality of the combination is like that of the individual drug ingredients.[3]

Medical
There should be a therapeutic justification for combining the active ingeidients. Event of the individual side effect in sepration should not be indications for the FDC.[3]

Interpretation of the results of Bioavailability (BA) and Bioequivalence (BE) Tests:
This includes both quality and therapeutic considerations. it is not satisfactory that the bioavailability of the fixed dose combination is decreased or variable when compared with that of single drug components because of poor formulation but an interaction between two active ingredients that pramotes to an expanded bioavailability may be one of the advantages that are considered when adjusting advantages and disadvantages.[3]

FIXED DOSE COMBINATION MARKET IN TOP REGULATED COUNTRIES

There has been an explosion of fixed dose combination drugs in India as pharmaceutical companies try to increase market share.

- Its revenue in India from combination drugs in 2014 was 24.62 billion rupees ($367 million), according to IMS Health.
- In the United States FDCs made up 13.9% of drugs on the market, while in China the number was 14.4%, according to IMS Health in 2014, about 78% of combination drugs in India.[5]

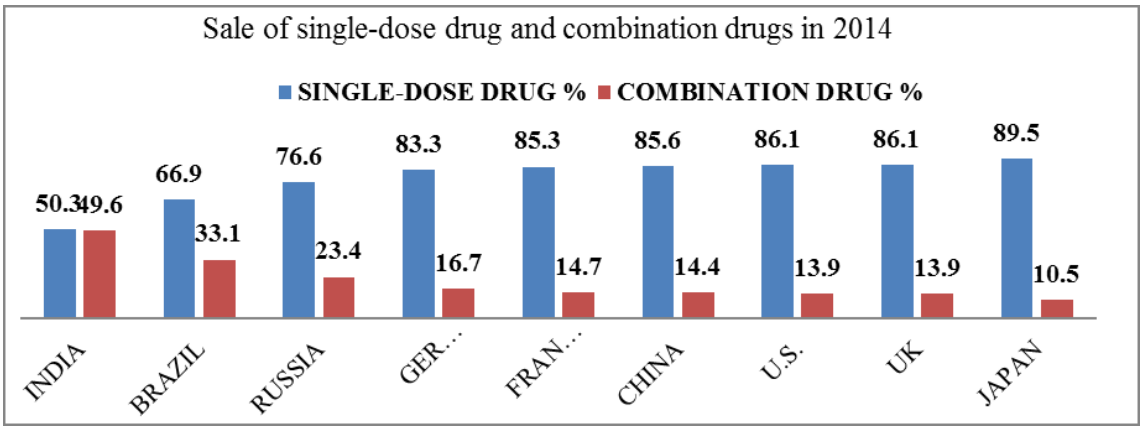


Figure 1: Sale of single-dose drug and combination drugs in 2014, (Source: IMS Health)

FEW FIXED DOSE COMBINATIONS IN ESSENTIAL LIST OF MEDICINES

Essential medicines are those that fulfill the priority health care needs of the population and intended to be available at all times, inadequate amount and at an affordable price. The list is prepared with due consideration to disease prevalence, efficacy, safety and comparative cost-effectiveness of medicines. Out of the 414 medicines included in the 19 list of WHO List of Essential Medicines, 27 are FDCs. We included 24 FDCs out of 376 medicines in the National List of Essential Medicines of India (NLEM) 2015.[2, 6-7]

REGULATORY PROVISIONS FOR FDCs IN INDIA

Appendix VI of Schedule Y (Drugs & Cosmetics Rules 1945, India) provides details about the requirements for manufacture/import approval and marketing of various types of FDCs. as per the Rule 122E of Drugs and Cosmetics act 1940, the fixed dose combination (FDCs) is considered as New Drugs and the Central Drugs Standard Control Organization (CDSCO), after due examination of data on rationality, safety, efficacy and issues approval. [4, 8]

DRUG APPROVAL PROCESS IN INDIA

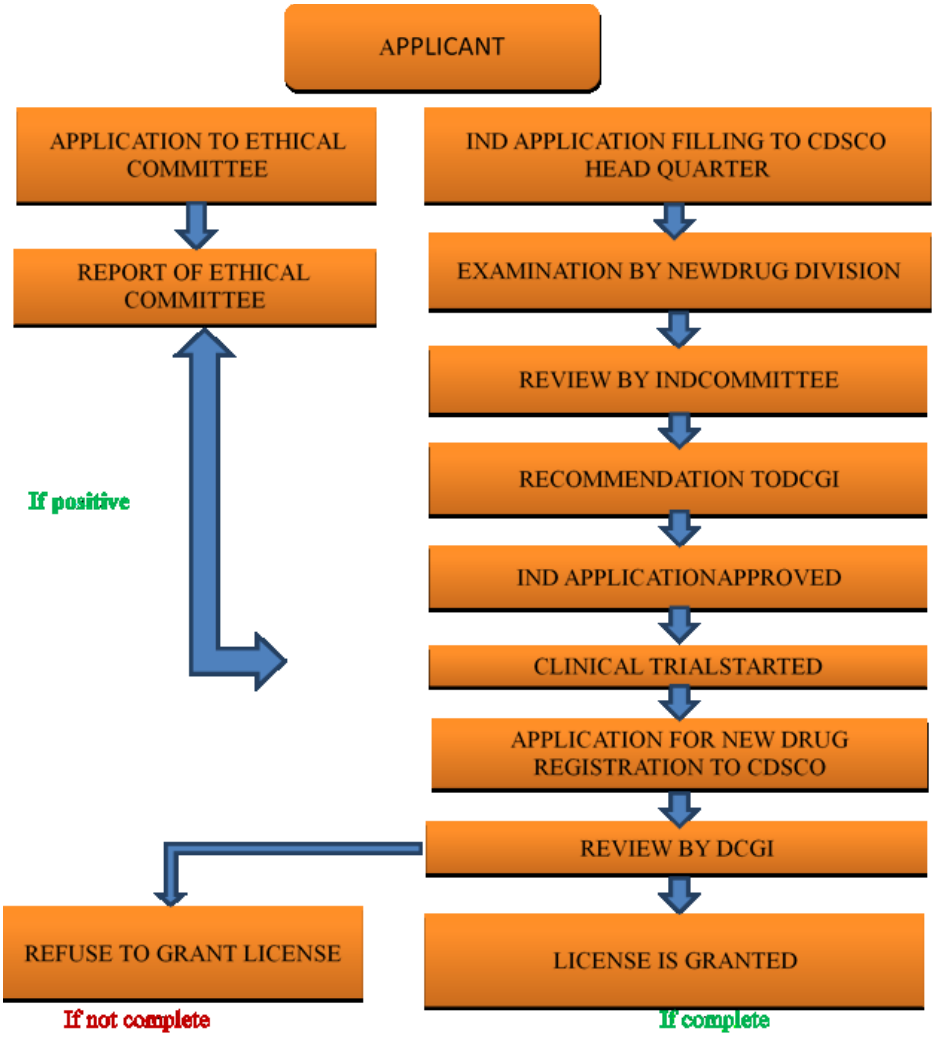


Figure 2:Pictorial representation drug approval process in India

DATA FOR APPROVAL OF FIXED-DOSE COMBINATIONS

Table 1:Data requirements for approval of fixed-dose combinations

S.No.	Requirements	Category I	Category II		Category III		Category IV
			A	B	A	B	
1.	Form 44	✓	✓	✓	✓	✓	✓
2.	Treasury Challan	✓	✓	✓	✓	✓	✓
3.	Justification as Annexure 1	✓	✓	✓	✓	✓	✓
4.	Source of bulk drugs	✓	✓		✓	✓	✓
5.	Strategies towards PMS as Annexure 4	✓	✓	✓	✓	✓	✓
6.	Scientific literature supporting the claim as Annexure 2	✓	✓	✓	✓	✓	✓
7.	Risk benefit assessment of combination	✓	✓	✓	✓	✓	✓
8.	Regulatory approval for the APIs	✓		✓	✓	✓	
9.	Regulatory approval of FDC		✓				✓
10.	Free sale certificate from the country of origin	✓	✓	✓	✓	✓	✓
11.	Complete chemical and pharmaceutical data of FDC	✓	✓	✓	✓	✓	✓
12.	GMP certification of manufacturing plant	✓	✓	✓	✓	✓	✓
13.	Certificate of analysis of study drug(s)	✓	✓	✓	✓	✓	✓
14.	Copy of proposed package insert	✓	✓	✓	✓	✓	✓
15.	Copy of package inserts and promotional literature		✓		✓		✓
16.	Clinical and non-clinical study reports	✓					
17.	Reports of bioequivalence studies as Annexure 7		✓		✓	✓	✓
18.	Acute and sub acute toxicity data in case of injectable formulation		✓	✓	✓	✓	✓
19.	In-vitro studies data				✓	✓	

CLINICAL DATA REQUIREMENTS FOR (NEW FDCs)

a. Clinical studies to be intended to figure out whether the combination has an advantage over the single active components.
b. The study should be conducted in the appropriate patient population with an adequate sample size to give the study 80% power and an alpha error of 5%.
c. The studies should be planned so that there is regional representation to all populations in the country.
d. The sites should be approved by the DCGI
e. Sites should have Institutional Ethics Committees registered with the CDSCO.
f. The data should preferably demonstrate that each actively contributes to the therapeutic effect of the combination.
g. The choice of comparators for the purpose of safety and efficacy studies.[3, 4, 9]

DATA REQUIRED FOR PHARMACOVIGILANCE FOR FDCS

a. Safety data from clinical development
b. All the potential risks of an FDCs
c. Summary of anticipated risks
d. All the potential drug - drug and drug – food interactions of the FDCs either as a different document with pharmacovigilance plan or pharmacovigilance strategies or in the section referring to data on safety details of the Common Technical Document (CTD)
e. Protocols for comparative observational studies.[3, 4, 9]

DATA REQUIRED FOR THE CONDUCT OF BIOAVAILABILITY (BA)/BIOEQUIVALENCE (BE) STUDIES

a. Title of the study, the protocol code.
b. Name of the Investigational product tested, development Phase, indication studied.
c. A brief description of the trial design.
d. The start and end date of patient accrual.
e. The start and end date of sample analysis.
f. The names of the Sponsor and the participating Institutes (Investigators).
g. Names and batch numbers of the products compared.[3, 4, 9, 10]

RECENTLY APPROVED FIXED DOSE COMBINATIONS BY DCG(I) IN 2016

Table 2: Recently Approved Fixed Dose Combinations by DCG(I) In 2016(Source: CDSCO)

S.NO.	Name of Drug	Indication	Date of approval
1.	Teneligliptin Hydrobromide Hydrate Eq. to Teneligliptin 20mg Metformin- 500mg/1000mg (ER) Tablets	Improve glycemic control in adults with type 2 diabetes mellitus	5.01.2016
2.	Emtricitabine 200mg Tenofovir Disoproxil Fumarate 300mg eq. to Tenofovir Disoproxil 245mg Tablet	Used for human immunodeficiency virus (HIV)	17.02.2016
3.	Brinzolamide - 1.0% w/v Timolol maleate – 0.683% w/v Eq. to Timolol 0.5% w/v suspension	Ophthalmic suspension	18.02.2016
4.	Rifampicin - 75mg Isoniazid -50mg Pyrazinamide -150 mg dispersible tablet	treatment of tuberculosis in children	08.03.2016
5.	Rifampicin 75mg Isoniazid 50mg dispersible tablet	treatment of tuberculosis in children	11.03.2016
6.	Clopidogrel Bisulphate eq. to Clopidogrel 75mg	treatment of angina and myocardial infarction	15.03.2016
7.	Brinzolamide 10mg Brimonidine Tartrate eq. to Brimonidine 2mg suspension	Ophthalmic suspension	30.03.2016
8.	Each Hard gelatin capsule contains: Rosuvastatin calcium IP + Choline Fenofibrate IP	treatment of mixed dyslipidemia	16.06.2016
9.	Each Hard Gelatin Capsule contains: Rosuvastatin Calcium + Aspirin (as enteric coated tablet) 75mg/150mg	treatment of dyslipidemia associated with atherosclerotic arterial disease .	08.08.2016

RECENTLY BANNED FDCS

To make a study on FDCs the central government had appointed an expert six-member committee headed by Chandrakant Kokate. FDCs have some disadvantages which led to ban the FDC in India

- Out of the 6,220 FDC samples that were taken up by the committee, 963 FDCs have been found irrational after a year of study, but the government decided to ban only 344.
- Due to this sudden prohibition, the Indian pharmaceutical industry suffered an enormous loss of 3000Crore, which accounts for 3% of the pharmaceutical market. [12, 13, 14]

RECOMMENDATION TO THE GOVT.

- Indian market is flooded with many irrational formulations/combinations and western markets such United States and Europe are very cautious in giving approvals for FDCs.
- Pharma Industry should work responsibly ensuring the satisfactory justification data of efficacy and safety to develop FDCs.
- Absence of stringent regulations, appropriate drug approval processes is the reason for such irrational drugs in Indian market.
- Pharmacovigilance and adverse drug monitoring should be necessary to assess the performance of the drug product in the clinical practice
- No systematic guidelines are available to the United States, European and Indian regulatory authorities with respect to antidiabetic and antihypertensive FDCs. Approvals were given on a case to case basis and available general guidelines for medicinal products with regard to efficacy, quality and safety.[15,16,17]
- Medical education on drug information, training medical and pharmacy students with an orientation to the public health implications of FDCs misuse.
- Good prescribing and pharmacy practices will go a long way in addressing the attitude, knowledge and practice gap of practicing physicians and pharmacists.

CONCLUSION

The above review concludes that all regulatory data and information related to the approval of fixed-dose combinations

(FDCs) in India ought to give the essential necessities alongside the market authorization application (MAA) to central drug standard control organization (CDSCO).It is likely such measures would improve the transparency, consistency, predictability and effectiveness of the regulatory processes along with reducing the unnecessary regulatory burden and promoting industrial compliance. this accommodates a scientifically solid method of building up the quality, safety and efficacy of therapeutic products.

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