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Fixed Dose Combinations Banned in India - A Review

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Abstract:

In our world we all depend upon medicines to cure and prevent the diseases, it may be single-drug therapy or a combination of drug therapy. The improvisation of Fixed-Dose Combinations (FDCs) is becoming more necessary from the public health aspect. In recent years for easy usage and higher efficacy FDC drugs are mostly used. Ministry of Health & Family Welfare (MoHFW) constituted a committee for inspecting the safety and efficacy aspects of FDCs which are unapproved were licensed by State drug Licensing Authorities (SLA) without due approval of Drug Control General of India (DCGI), after that committee discussed total 1083 FDCs which considered as irrational under category 'a' based on the report initially 344 FDCs were banned by DCGI. This review discusses about the reasons for ban, FDCs benefits, problems associated, approval process and its impact towards the most reputed companies.

Keywords: Fixed-dose combinations, Approval process, Banned drugs, Current status

INTRODUCTION

Fixed-dose combination (FDC) definition as per World Health Organization (WHO) states that, a combination of at least two active ingredients in a fixed proportion of ratio. This term is utilized conventionally to determine a blend of active ingredients regardless of the definition or brand. It might be managed as a single substance item given simultaneously or as a completed pharmaceutical item. Fixed-dose combinations (FDCs) are medicines containing two or more active components in a fixed proportion in a single dosage form. Several medicines in fixed combination to be taken together, presented in composite packaging (co-pack) [1]. FDC drugs are important for the public health perspective and commonly used for the treatment of pain, inflammation, hypertension, diabetes, malaria, tuberculosis, HIV/AIDS, etc.., FDCs important in patients suffering from multiple disorders and it reduces "pill burden".

The FDCs are advocated when they show clear benefits as far as:

- Potentiating the therapeutic efficacy,
- Minimizing the frequency of an unfriendly impact of medications,
- Having pharmacokinetic benefit,
- Better consistency by diminishing the pill trouble,
- Reducing the portion of individual medications,
- Decreasing improvement of opposition, and
- Cheaper than individual medication as a result of diminished expense from bundling to conveyance.

The above claims must be adequately supported by scientific evidence[2].

DISCUSSION

The Problems with Fixed-Dose Combination:

- A pharmacokinetic (PK) and pharmacodynamic (PD) mismatch between the two segments, one medication having added substance/hostile impact prompting diminished adequacy or upgraded harmfulness,
- Peak efficacy at various time interval,
- Chemical incongruence prompting reduced shelf life of realistic usability,
- Drug interactions and
- Dose limitations[3].

Chronology of Fixed Dose Combination:

FDC was first approved in 1961 by the DCGI, about more than 1,200 of combination drugs were approved as per the published list in the website of CDSCO. But FDCs have been approved by the State level basis but without the central government approval. It was not until 1988 that the "new drug" definition under Indian law was amended to include the combination of two or more drugs which was approved already. Since 2002 the law has been cleared which was said by the drug regulatory official. That year, an amendment to the statute explicitly stated that to make a new drug, a requirement of a prior written approval needed by the company of the central government in support of a state license application. Some of the pharmaceutical manufacturers who maintained the requirement that was not clear until 2012[4].

Drug regulator of India (CDSCO) came out with the policy guidelines for the approval of FDCs in 2013. CDSCO has periodically banned various FDCs due to reasons such as lack of rationale or evidence and potential safety concern. In 2007, the DCGI issued edict to all SLAs to withdraw 294 FDCs which were not approved by CDSCO. However, the industry disputed the ban and the matter is currently subjected[5].

The Parliamentary Standing Committee (PSC) on its 59th report have shown that manufacturing licenses issued by State Licensing Authority (SLA) for FDCs without past clearance from DCGI. Subsequently, the DCGI issued a circular on January 15, 2013, organizing the manufacturer's responsibility to ensure the safety and efficacy of FDCs, which was licensed by the SLAs before October 1, 2012, within 18 months; if it fails they would be considered as stopped from manufacturing and marketing in India. The FDCs approved before the year 1988 were exempted. In response, from the industry 6220 applications were received[6].

On September 16, 2014, the Ministry of Health and Family Welfare (MoHFW) arranged a committee for inspecting and analyzing the applications for the

reasonable, safety and efficacy of the FDCs. The committee was submitted its report to the MoHFW on April 16, 2015. Accordingly, letters were sent to submit phase 4 trial protocol to the manufacturers. Replies from manufacturers against show-cause notices concerning 1083 irrational FDCs under the category "a" were examined and the recommendations were submitted on February 10, 2016. Based on expert panel findings, on March 10, 2016, 344 FDCs were prohibited under Section 26A of Drugs and Cosmetics Act, 1940[7].

New drug definition according to rule 122E:

A medication, characterized by the Act which incorporates mass medication substance, which has not been utilized in the nation to any huge purpose of degree under those conditions endorsed, prescribed or recommended in the naming there of and which has not been perceived as viable and safe by the authorizing authority was referenced under Rule 21 for the proposed cases, accommodated the restricted use, assuming that has been with the authorization of the permitting authority[8].

A medication which was affirmed by the permitting authority, that referenced in Rule 21 for specific cases, which is currently proposed to be showcased with changed or new guarantees, in particular signs, dose, measurement structure (continued discharge dose structure likewise included) and course of the organization. A fixed-portion blend of at least two medications, affirmed separately in prior for specific cases, which are currently proposed to be joined for the underlying time in a fixed proportion or if the proportion of fixings in a previously promoted mix is proposed to be changed, with specific cases, signs, measurements, dose structure (counting supported discharge dose structure) and course of organization[9].

Various categories of FDCs and approval process:

Categories of FDCs:

All new drugs are required to abide by the provisions and requirements of Schedule Y to register in India. In Appendix VI of Schedule Y, the registration requirements for FDCs explained based on categories of FDCs.

1) FDC - In India, not marketed and one or more active ingredients is a new drug basis but not approved.

Subcategory I *- A combination in one of the ingredients is an Investigational New Drug (IND).*

Subcategory II *- A combination of the ingredients is a new drug that is not approved individually in India, however the same basis was approved in the other countries.*

2) FDC – Not marketed in India but their Active Pharmaceutical Ingredients are approved and having significant interactions on PK/PD.

Subcategory I *– FDC which are Marketed in abroad*

Subcategory II *– FDC which were not marketed as a product anywhere but as a individual components were used.*

Subcategory III *– FDC not marketed and individual components are not used.*

3) FDC – Which are marketed in India but some of the changes are obtained.

4) FDC – Only for comfort.

5) FDC – Approval of an FDC which are already approved in the country[10].

Approval Process:

Documents those necessary for the approval of an FDC vary widely depending on the category to where it falls, the characteristics of the drugs, disease for which it is specified, etc. To streamline the submission, CDSCO introduced a system of preliminary scrutiny of application at the time of receipt of the applications to determine the acceptability for review by CDSCO.

During the starter assessment, the CDSCO officials will examine the application to guarantee that it contains all the required regulatory just as specialized data in a legitimate way according to the agenda. If the application isn't submitted as per the organization and the agenda, it won't be acknowledged by CDSCO for further audit. If the application is acknowledged, the ampleness of the information will be looked into by CDSCO according to the predetermined necessities and rules.

On the off chance that the information submitted isn't sufficient, the candidate will be mentioned to create/submit satisfactory information for thought and endorsement of the FDC. The timeline for completion of the approval process for FDC is 180 days. On 14th November 2015, CDSCO launched the "SUGAM" portal for online application[11].

While examining the replies to the showcase notices of such FDC, committee considered the following points:

- Patients Safety
- Drug toxicity
- Misuse of drug
- Prescription error
- Pharmacokinetic and Pharmacodynamic incompatibility
- Antimicrobial drug resistance issue
- Latest Standard Treatment Guidelines (STG)
- Risk ratio
- Patient compliance
- International status

Market impact on FDC ban:

The ban will harm the growth of Indian pharmaceutical sector and it will not only affect revenues, turnover and profitability of the drug companies but also weaken their research and development (R&D) capability. According to analysts, the ban could cast Indian pharmaceutical companies about Rs. 3500 to 3800 crore. Sudden ban orders on formulations, which are widely prescribed and used, create confusion among physicians and patients. It reduced the availability of a drug with no alternative medication available in the market for various diseases. Chemists have warned the government that the recent ban on 350 FDCs would lead to a shortage of almost 5000 medicines, including generics from the market. As per the survey of a health advocacy platform (eMediNexus) around 80% of the doctors were found to prescribe drugs from the list of 344 drugs before the ban. As per the IMS

Health's market reflection report for June 2016, the banned FDCs market was altogether valued at Rs 3535 crore in June, with respiratory drugs capturing 44 percent of the overall value[13].

Top brands affected by FDC ban:

1. Pfizer is about to take a great hit as its popular cough syrups - Corex and Corex-DX are among one of the banned brands. This combination of 2 brands had annual sales of Rs 423 crore (Rs 4.23 billion).
2. Abbott's 3 major cough syrups such as Phensedyl, Tixylix and Tossex which had annual sales of Rs 290 crore (Rs 2.9 billion), were stopped by the officials of the government body.
3. Macleods Pharma's skin cream Panderm+ has also been banned. This particular cream having worth of Rs 228.2 crore to the company in annual sales.
4. Lupin's anti-diabetic drug Gluconorm-PG, which had sales of Rs 46.5 crore, has also been banned[14].

Approval process:

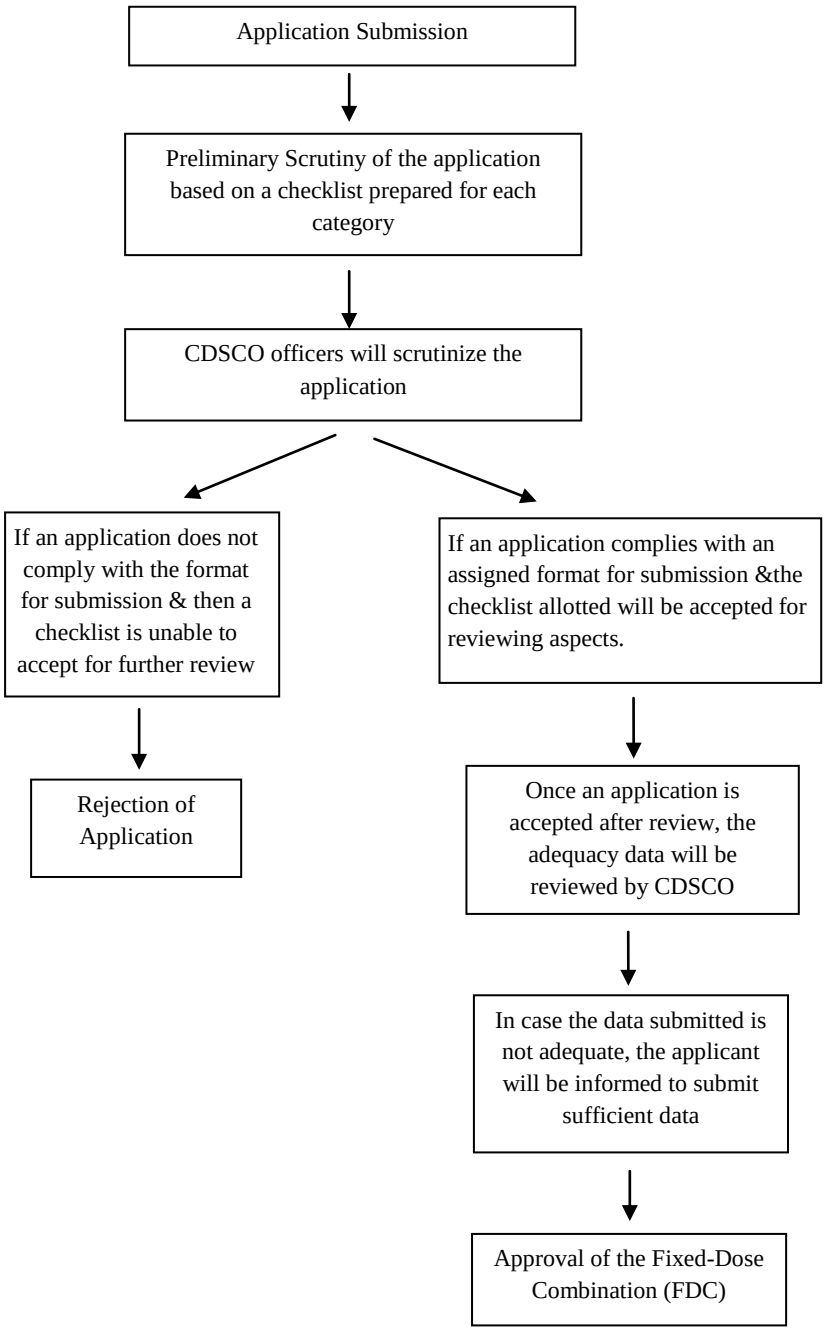

Figure 1: Approval process of FDC[12]

Table 1: Major Companies losses based on disease conditions[15]

Categories of impact (in crore)		Companies losses (in crore)	
Respiratory	1,308	Abbott Healthcare	485
Anti-diabetic	609	Macleods Pharma	370
Pain/ analgesics	550	Pfizer	368
Anti-infective	519	Mankind	253
Gastrointestinal	485	Alkem	161
Derma	279	Ipca	130
Neuro/CNS	49	Medley	116
Gynaecological	30	Glenmark	110
Blood-related	3	Franco	104
Urology	1	Wockhardt	102
Cardiac	1	Aristo	102

Pfizer - Corex cough syrup:

In March 1995, Pfizer got a license for manufacture and sale of Corex from the drug controller. Corex cough syrup composition changed finally in 1995. Corex falls under Schedule H-1 of the Drugs and Cosmetics Rules, 1945. Corex can be sold to the users only when medical practitioners prescribed it. Similar pharmacological compositions are being sold in the USA, EU, UK and Australia[16].

Composition of Corex cough syrup:

Chlorpheniramine maleate, Codeine phosphate, Carmoisine and sunset yellow CPF as colorants. The closeness of Chlorpheniramine maleate in the subject medication is vital since it is an anti histamine for pacifying histamine-actuated unfavorable susceptible edema (or) respiratory mucosa. Codeine phosphate the subject medication is fundamental since it is an anti tussive. Chlorpheniramine maleate anticipates the nasal and bronchial discharges which would bother the organs in the throat in this way prompting dry hack. Codeine phosphate stifles the organs, lessen hack reflexes. That the blend works viably as both the fixings supplement one another. Such prompt restriction on Corex and other comparative mixes that had been in the market for more than 25 years is illicit. More secure choices are accessible and no such options have been unveiled in the notification. That regardless of whether more secure choices are accessible, a sensible period is required to receive the equivalent[17].

Current status based on DCGI order:

DCGI order to all FDCs manufacturers to submit Periodic Safety Update Report (PSUR) within 18 months from the final judgment.

Key recommendations:

- To prove scientifically the safety and efficacy of the combination by conducting clinical trials as per Schedule-Y
- To implement composition changes as per the approved list with all safety details.
- The subject 344 drugs should be taken into DTAB for analysis and should be scrutinizing the 344 combinations individually based on the safety and efficacy parameters.
- Legally approach the same cases of FDCs after development in Supreme Court with hope, Since the 344 drugs are banned in Delhi High Court based on procedural lapse[18].

CONCLUSION

The overall methodology of FDC analysis should be based on more scientific approaches which should also involve clinical trials in the Indian population (Multicentric clinical trial). Medical fraternity & Pharm D (clinical pharmacists) should place an important role in deciding the dose and time duration of each drug which is consumed by the patient prescribed by a doctor in case of chronic therapies such as diabetes, hypertension, and infectious diseases. Pharmaco-vigilance department is mandatory to study the safety & efficacy of drugs before and after the approval of drugs (Post-marketing surveillance). The development of FDCs is becoming much important from a public health point of view. In recent years for easy usage and higher efficacy fixed-dose combination drugs are mostly used but because of lack of coordination between State & Central Regulatory bodies, all these issues were developed it should be rectified and transparency should be maintained in all aspects of the regulatory process. The Process of regulation must be strengthened.

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Conflict of interest:

The authors declare no conflict of interest.

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