

Ban of Fixed Dose Combination on India: Impact and Implications

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ABSTRACT

Fixed dose combinations (FDCs) of drugs are important for public health perspective and commonly used for the treatment of pain & inflammation, hypertension, diabetes, malaria, tuberculosis, HIV/AIDs etc. These ailments are considered to be the foremost threats to health in the world today. FDCs have proved to be advantageous as they are safe and effective. They increase efficiency, reduce the incidence of adverse drug effects, and improve patient compliance. The FDCs offer low cost as compared to individual components of active ingredients. On other hand if administered in unprofessional way, FDCs have given problem of drug resistance in the case of antimicrobial treatment especially in case of treatment of tuberculosis malaria. In some instances wrong understanding of FDCs have been proved to be fatal.[1]

The FDCs being extensively used for so long for various ailments in order to get combination of drugs for a particular disease at low cost. Doctors appreciated the use of FDCs in their practice. Then problems started arising about the irrational use and safety profile of these drug combinations, which makes regulatory bodies to take action against the use of FDCs. Petitions being filed in supreme court against the ban imposed on FDCs by regulatory bodies by the pharma companies. At the end 15 FDCs were spared to be banned and rest 328 FDCs were banned to be manufactured, market and sale.

The article aims at identifying the reasons behind banning the fixed dose combinations and the impact of the ban on pharma market.

KEYWORDS: FDCs (Fixed Dose Combinations), Public Health, Irrational use of FDCs, Ban on FDCs

INTRODUCTION

Medicines are an integral part of healthcare. More than one drug is frequently used for treatment of either single ailment or multiple comorbid conditions. Sometimes, two or more drugs are combined in a fixed ratio into a single dosage form, which is termed as fixed dose combinations (FDCs). The FDCs are justified when they demonstrate clear benefits in terms of (a) potentiating the therapeutic efficacy, (b) reducing the incidence of adverse effect of drugs, (c) having pharmacokinetic advantage, (d) better compliance by reducing the pill burden, (e) reducing dose of individual drugs, (f) decreasing development of resistance, and (g) cheaper than individual drug because of reduced cost from packaging to distribution. It is important that the above claims are adequately supported by scientific evidence.^[2]

According to CDSCO, Fixed Dose Combinations refer to products containing one or more active ingredients used for a particular indication(s). FDCs can be divided into the following groups and data required for approval for marketing is described below:

1. The first group of FDCs includes those in which one or more of the active ingredients is a new drug. For such FDCs to be approved for marketing data to be submitted will be similar to data required for any new drug (including clinical trials)

- 2. The second group 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 interaction of a pharmacodynamic or pharmacokinetic nature. If clinical trials have been carried out with the FDC in other countries, reports of such trials should be submitted. If the FDC is marketed abroad, the regulatory status in other countries should be stated.
- A. For marketing permission, appropriate chemical and pharmaceutical data will be submitted. In case such a combination is not marketed anywhere in the world but these drugs are already in use concomitantly (not as an FDC but individually) for the said claim, marketing permission may be granted based on chemical and pharmaceutical data. Data showing the stability of the proposed dosage form will also have to be submitted.
- B. For any other such FDCs, clinical trials may be required. For obtaining permission to carry out clinical trials with such FDCs a summary of available pharmacological, toxicological and clinical data on the individual ingredients should be submitted, along with the rationale for combining them in the proposed ratio. In addition, acute toxicity data (LD 50) and pharmacological data should be submitted on the individual ingredients as well as their combination in the proposed ratio.

3. **The third group of FDCs** includes those which are already marketed, but in which it is proposed either to change the ratio of active ingredients or to make a new therapeutic claim. For such FDCs, the appropriate rationale including published reports (if any) should be submitted to obtain marketing permission. Permission will be granted depending upon the nature of the claim and data submitted.
4. **The fourth 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. It will have to be demonstrated that the proposed dosage form is stable and the ingredients are unlikely to have significant interaction of a pharmacodynamic or pharmacokinetic nature. No additional animal or human data are generally required for these FDCs, and marketing permission may be granted if the FDC has an acceptable rationale.^[3]

LOGIC BEHIND FDCS

The logic behind FDCs is to improve adherence, simplify therapy and/or to maximise benefit for the patient courtesy the added effects of the multiple medicinal products given together. Popular FDCs, now banned, include the painkiller Saridon, the skin cream Panderm, antibiotic Lupidiclox and combination diabetes drug Gluconorm PG.

A government document titled '**Policy Guidelines for Approval of Fixed Dose Combinations in India**', released in June 2013 had claimed that "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."

For instance, several FDCs pack a combination of Nimesulide and paracetamol and are sold under different brand names as an anti-pyretic, or medications to control fever.

India reportedly boasts around 2,000 FDCs, four times more than what's available in the US.^[4]

THE GOOD, THE BAD, AND THE UGLY OF THE FIXED DOSE COMBINATION IN INDIA

On the basis of the rationality of available FDCs in India, we are tempted to classify them as follows:

The Good FDCs – having strong justification, for example, carbidopa + levodopa, sulfonamides + trimethoprim, antitubercular drugs, antiretroviral drugs, some antihypertensives, and some antidiabetic medications;

The Bad FDCs – are formulated primarily with marketing interests and do not add any value to the therapeutic usefulness and whose justification is debatable. Majority of the available FDCs fall in this category. Some examples are combinations of dual nonsteroidal anti-inflammatory drugs (NSAIDs), NSAIDs with muscle relaxant, and NSAIDs with H2 blockers.

The Ugly FDCs – those that have neither evidence nor theoretical justifications. There could be a possibility of adverse event because of wrongful administration of an

unnecessary component, or where the dose titration is required. Some examples of such bizarre combinations are formulations having cough syrups with two or more antihistamines + decongestant + bronchodilator + cough suppressant + expectorant and antifungal + antibiotic + steroid + topical local anesthetic.

Due to the difficulties in developing new chemical entities, the pharmaceutical industry finds it easier to develop FDCs. India is primarily the market of generic drugs. As the patent expires, the intense competition among multiple manufacturers tempts them to give the product a new look claiming multiple advantages without scientific validation. By the **Drug Price Control Orders 2013**, the drugs included in the **NLEM** (National list of Essential Medicines) were brought under price control by the National Pharmaceutical Pricing Authority of India. To evade the price control, some companies reformulate the individual drugs into an FDC. This loophole has since been checked.^[5]

GOOD FDCs	BAD FDCs	UGLY FDCs
Have strong justification	Have debatable justification	Have neither evidence nor justification

RATIONAL AND IRRATIONAL FDCs

The general acceptance is that most drugs should be formulated as single compounds. However, as we discussed above, there are certain circumstances when FDCs are logical to be used. On the basis of few criteria, the WHO defines the FDCs as rational or irrational. **A rational Fix ratio combination of drugs** is when:

- The combination of ingredients meets the requirements of a defined population group.
- Such combo has proved to be to be definitely advantageous over single compounds.
- The drug in the combination should act by different mechanisms and their mix should not result in supra-additive toxicity.

Some of the examples of rational FDCs include sulfamethoxazole + trimethoprim; rifampicin + isoniazid, isoniazid + ethambutol etc. (used in TB); levodopa + carbidopa (used in Parkinson's disease) etc.

However, **when the above given criteria are not met, the FDCs would be termed irrational.**

One example of irrational FDCs is Nimesulide + paracetamol formulations for children. Both Nimesulide and paracetamol reduce fever and are anti-inflammatory; and Nimesulide is in fact more effective than paracetamol. This irrational combination puts the children on risk and provides no additional benefits. Thus, it is the mushrooming of irrational FDCs which creates a problem. There are numerous examples which we come across every day of FDCs such as Ibuprofen + paracetamol, cefixime and azithromycin etc.^[6]

Fixed-dose combination (FDC) medicines, which are a cocktail of two or more active drugs packed in a single dose, are in the spotlight currently due to government's ban on them. The domestic pharmaceutical market size is pegged at around Rs 1.18-1.2 lakh crore, and FDCs reportedly make up nearly 50% of the sales.^[6]

ADVANTAGES OF FDC

- Simpler dosage schedule improves compliance and therefore improves treatment outcomes
- Reduces inadvertent medication errors
- Prevents and/or slows attainment of antimicrobial resistance by eliminating monotherapy (i.e, one drug is never by itself in circulation)
- Allows for synergistic combinations (i.e., trimethoprim/sulfamethoxazole combination allows each drug to selectively interfere with successive steps in bacterial folate metabolisms
- Reduces drug shortages by simplifying drug storage and handling, and thus lowers risk of being "out of stock"
- Only 1 expiry date simplifies dosing (single products may have different expiry dates)
- Procurement, management and handling of drugs is simplified Lower production, packing and shipping costs
- Side effects may be reduced by using one drug of the combination for this purpose
- Potential for drug abuse can be minimized by using one drug of the combination for this purpose (i.e., excessive use of the antidiarrheal narcotic diphenoxylate is discouraged by side effects of atropine in the FDC atropine + diphenoxylate)^[7]

DISADVANTAGES OF FDC

- FDCs are sometimes more expensive than separate tablets, although not invariably so.
- Potential quality problems when drugs are combined, especially with rifampicin in FDCs for TB. This requires bio-availability testing
- If a patient is allergic or has a side-effect to 1 component, the FDC must be stopped and replaced by separate tablets, although this issue exists even with single dose formulations.
- Dosing is inflexible and cannot easily be regulated to patient's needs (each patient has unique characteristics such as weight, age, pharmacogenetics, co-morbidity, that may alter drug metabolism and effect). This criticism does not, however, apply to TB or HIV/AIDS where FDCs are made with weight-adjusted dosages .
- Incompatible pharmacokinetics is irrational because of different elimination $\frac{1}{2}$ lives of individual components.
- Drug interactions may lead to alteration of the therapeutic effect^[7]

REASON FOR EXTENSIVE USE OF FDCS

The one-word answer is cost. Instead of buying two, or more, separate medicines, a patient can buy just one FDC medicine to treat multiple illness symptoms, which typically works out easier on the wallet. Pharma companies, meanwhile, love them because it is far cheaper and quicker to combine existing active ingredients to make new products than to discover new medicines and manufacture them separately.

Amit Sengupta, national convener of Jan Swasthya Abhiyan, previously told The Hindu Business Line that another reason the Indian market was flooded with FDCs was because pharma companies preferred them to circumvent price control. "They [the companies] prefer to market FDCs that are not under price control rather than single-ingredient drugs under price control," he said, adding that 'me too' marketing was also to blame.

"Companies vie with one another for a share of the market for the same class of drugs. In order to provide something 'new' to prescribers, they develop and market FDCs (often

irrational, but promoted as a unique and innovative product by each company) purely for commercial reasons, and support its sales through sophisticated (and often unethical) marketing strategies," he had added.^[8]

Because of the extensive irrational use by consumer the govt, realize the need to take a corrective action on usage of FDCs

BAN ON FDC

Background

The health ministry has been gunning for "irrational" and "unsafe" FDCs for over two years . In March 2016, the government had banned 344 FDCs, adding five more to the list subsequently, following a report submitted by the Prof CK Kokate committee.

But drug makers, including Pfizer, Procter & Gamble, Abbott, Glenmark, Sanofi, Wockhardt, Cipla, Lupin and Dr Reddy's, had immediately moved various courts against the decision. The Delhi High Court alone had received over 450 petitions seeking a stay on the ban.

In December 2016, the Delhi High Court squashed the Centre's decision, noting that it had acted on the advice of a 'technical committee', instead of consulting the Drugs Technical Advisory Board (DTAB) or the Drugs Consultative Committee. According to the bench, this violated the provisions of the Drugs and Cosmetics Act.

The health ministry had challenged this ruling in Supreme Court and, in December 2017, the latter directed DTAB to decide the fate of these FDCs. Incidentally, the DTAB has recommended restricted manufacture and sale of six other FDCs, subject to certain conditions based on their therapeutic justification. The SC also ruled that the government could not use the DTAB report to prohibit 15 of the 344 drugs in the original list as these have been manufactured in India since before 1988.

According to The Times of India, this exception covers several popular cough syrups, painkillers and cold medication with sales amounting to over Rs 740 crore annually. However, the apex court told the ministry that it is free to initiate a fresh investigation into the safety of these 15 drugs if it wants them banned.^[9]

Government bans 328 FDCs: Recent Development

The health ministry took this decision after the Drugs Technical Advisory Board recommended that "there is no therapeutic justification" for the ingredients contained in the banned FDC drugs and that these medicines "may involve risk to human beings".

Health experts have long maintained that many FDC combinations in the market neither boast any advantage over individual drugs nor are safe. Simple logic dictates that chances of adverse drug effects and drug interactions can go up if medicines are combined instead of being taken separately. Apart from the fact that some of the drugs reportedly boast dangerous side-effects, unnecessary use of combination drugs makes the human body resistant to treatment.

Worryingly, published studies have long claimed that FDCs are often prescribed to cover up for diagnostic imprecision-likely making them extremely popular with quack doctors. Hence, in a bid to stop the irrational use of FDCs, the Union Health Ministry banned the manufacture, sale or distribution

of 328 varieties of FDC drugs for human consumption. **The move likely affected over 6,000 medicine brands.**

"The banned FDCs account for about Rs 2,500 crore and represent only the tip of the iceberg. In our estimate, the market for unsafe, problematic FDCs in India is at least one-fourth of the total pharma market which is valued at Rs 1.3 trillion," the All India Drug Action Network, a civil society group working on safety and access to medicines and one of the petitioners in the Supreme Court case, said in a statement.^[10]

IMPACT OF BAN OF FDCS ON PHARMA MARKET:

Large pharma companies had reportedly said that the impact was expected to be negligible since the FDCs in question are less than 2% of the pie. They added that over the last couple of years, they have either phased out such drugs or changed the combination.^[12]

An FDC contains two or more drugs combined in a fixed ratio, and made available in a single dosage form. They comprise around 50% of the Rs 1.25-lakh-crore market (moving annual total, or MAT, June 2018), with only certain combinations being marketed "irrational" and "harmful".^[11]

BITTER PILL
Of the total ₹1.25L-cr Indian pharma market, the ban affects drugs worth ₹2,900cr, or over 2%

Supergroup (in ₹ cr)	Not banned	Banned	Total*	Impact (in %)
Respiratory	8,895	1,038	9,933	10.4
Anti-diabetic	11,048	568	11,617	4.9
Ophthalmologicals	2,327	84	2,412	3.5
Derma	9,144	327	9,471	3.4
Anti-infectives	14,880	424	15,304	2.8
Hepatoprotectives	1,319	31	1,350	2.3
Gynaec	5,975	108	6,083	1.8
Pain/analgesics	9,591	129	9,720	1.3
Anti-parasitic	360	5	364	1.3
Gastro-intestinal	13,088	115	13,203	0.9

*Total Indian pharma market Source: IQVIA

Image 1: Therapeutic segments most likely affected by FDCs ban^[13]

Last year, the Supreme Court (SC) had asked the DTAB to review the matter and recommend which FDCs should be regulated or banned, following a protracted legal battle between the government and drug companies over the issue.

The banned combinations on the proposed list belong to several therapeutic areas like cough and cold syrups, gastrointestinal and anti-infective formulations, and dermatological medicines. The respiratory portfolio will bear the highest impact of 10%, followed by antidiabetic and anti-infective drugs Gastro-intestinal medicine Panderm+ (Macleods Pharma) is the most impacted brand at 8% or Rs 233 crore in value terms in the banned category, followed by cough preparation Phensedyl Cough (Abbott).^[12]



Image 2: List of top 5 companies which got affected by ban on FDCs^[14]

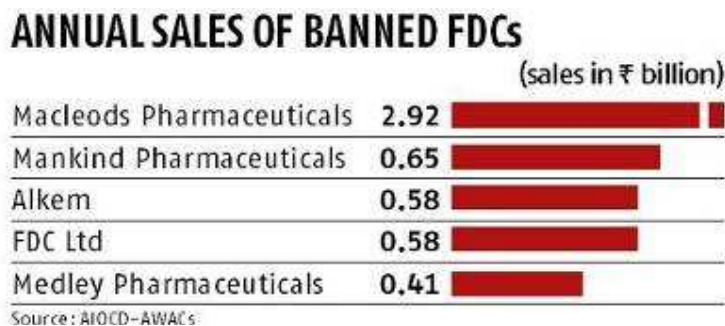


Image 3: impact on sales of banned FDC^[15]

CONCLUSION

Fixed dose combinations were found to be of great use due to the benefits related to cost and simple dosage schedule however due to reported cases about lack of safety and irrational use and the manufacturing of fixed dose combinations, which were not worth, by the pharma companies, doctors started losing interest in using fixed dose combinations and the drug regulatory authorities took action about the irrationality of these combinations. As a result legal action has been taken and hence manufacturing, marketing, selling and prescription of about 328 fixed dose combinations had been banned by Supreme Court. This ban has affected about one-fourth of the total pharma market which is valued at Rs 1.3 trillion.

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