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An effort to comprehend the rationales behind the prohibition of fixed dose combinations

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ABSTRACT: Pharmaceuticals encompass compounds utilized for the purposes of disease treatment, alleviation, diagnosis, and prevention. The substances in question can be classified into three categories: synthetic, semi-synthetic, or natural. A condition can be treated either by a single treatment or by the separate administration of numerous drugs. Another approach involves the use of specific dosage forms that contain two or more pharmaceuticals, known as fixed dose combinations. The term "fixed dose combination" refers to the incorporation of many active components into a single mode of pharmacological administration. These products are highly sought after by both prescribers and consumers due to their numerous advantages. There are also inherent drawbacks that cannot be overlooked. This article examines both the advantages and disadvantages associated with the banning of numerous Fixed Dose Combinations (FDCs) by the Government of India, as outlined in the gazette. The primary focus is on identifying the underlying causes for these bans. Additionally, the study explores the perspectives of specialists regarding FDCs and their corresponding recommendations.

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INTRODUCTION:

Products combining one or more active substances and intended for a specific indication(s) are known as fixed dose combinations (FDC). Table 1 lists the various categories into which FDCs can be placed [1].

For reasons of public health, the government has banned the following FDCs from production, sale, and distribution in accordance with Section 26 A of the Drugs and Cosmetics Act of 1940. Table 2 provides a list of FDCs that have been banned [2].

The concurrent administration of Paracetamol and Ibuprofen. Paracetamol is classified as an analgesic, which refers to its ability to alleviate pain, and as an

Group I	The first group of FDCs includes those in which one or more of the active ingredients are a new drug.
Group II	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.
Group III	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.
Group IV	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.

Table 2. List of banned fixed dose combinations.

Sl. No.	Combinations	Notifi-cation in the gazette	Section	Date	Expert opinion
1	Nimesulide + Paracetamol dispersible tablets	S.O.712 (E)	Extraordinary, Part II, Section 3 (ii)	10 March 2016	There is no therapeutic justification for the ingredients contained in this FDC and the FDC may involve risk to human beings.
2	Amoxicillin + Bromhexine	S.O. 777(E)	Extraordinary, Part II, Section 3 (ii)	10 March 2016	There is no therapeutic justification for the ingredients contained in this FDC and the FDC may involve risk to human beings.
3	Pholcodine + Promethazine	S.O. 789 (E)	Extraordinary, Part II, Section 3 (ii)	10 March 2016	There is no therapeutic justification for the ingredients contained in this FDC and the FDC may involve risk to human beings.
4	Chlorpheniramine maleate + Dextromethorphan + Guaiphenesin + Ammonium chloride + Menthol	S.O. 869 (E)	Extraordinary, Part II, Section 3 (ii)	10 March 2016	There is no therapeutic justification for the ingredients contained in this FDC and the FDC may involve risk to human beings.
5	Chlopheramine maleate + Codeine syrup	S.O. 909 (E)	Extraordinary, Part II, Section 3 (ii)	10 March 2016	There is no therapeutic justification for the ingredients contained in this FDC and the FDC may involve risk to human beings.
6	Ammonium chloride + Bromhexine + Dextromethorphan	S.O 900 (E)	Extraordinary, Part II, Section 3 (ii)	10 March 2016	There is no therapeutic justification for the ingredients contained in this FDC and the FDC may involve risk to human

					beings.
7	Bromhexine + Dextromethorphan + Ammonium chloride + Menthol	S.O. 925 (E)	Extraordinary, Part II, Section 3 (ii)	10 March 2016	There is no therapeutic justification for the ingredients contained in this FDC and the FDC may involve risk to human beings.
8	Dextromethorphan + Chlorpheniramine + Guaiphenesin + Ammonium chloride	S.O. 930 (E)	Extraordinary, Part II, Section 3 (ii)	10 March 2016	There is no therapeutic justification for the ingredients contained in this FDC and the FDC may involve risk to human beings.
9	Paracetamol + Bromhexine + Phenylephrine + Chlorpheniramine + Guaiphenesin	S.O. 977 (E)	Extraordinary, Part II, Section 3 (ii)	10 March 2016	There is no therapeutic justification for the ingredients contained in this FDC and the FDC may involve risk to human beings.
10	Salbutamol + Bromhexine	S.O. 978 (E)	Extraordinary, Part II, Section 3 (ii)	10 March 2016	There is no therapeutic justification for the ingredients contained in this FDC and the FDC may involve risk to human beings.
11	Chlorpheniramine + Codeine phosphate + Menthol syrup	S.O. 986 (E)	Extraordinary, Part II, Section 3 (ii)	10 March 2016	There is no therapeutic justification for the ingredients contained in this FDC and the FDC may involve risk to human beings.
12	Phenytoin + Phenobarbitone sodium	S.O. 1028 (E)	Extraordinary, Part II, Section 3 (ii)	10 March 2016	There is no therapeutic justification for the ingredients contained in this FDC and the FDC may involve risk to human beings.
13	Ammonium chloride + Sodium citrate + Chlorpheniramine maleate + Menthol (100 mg + 40 mg + 2.5 mg + 0.9 mg), (125 mg + 55 mg + 4 mg + 1 mg), (110 mg + 46 mg + 3 mg + 0.9 mg) and (130 mg + 55 mg + 3 mg + 0.5 mg) per 5 ml syrup	S.O. 4411 (E)	Extraordinary, Part II, Section 3 (ii)	07 September 2018	There is no therapeutic justification for the ingredients contained in this FDC and the FDC may involve risk to human beings.
14	Salbutamol + Hydroxyethyl theophylline (Etofylline) + Bromhexine	S.O. 4687 (E)	Extraordinary, Part II, Section 3 (ii)	07 September 2018	There is no therapeutic justification for the ingredients contained in this FDC and the FDC may involve risk to human beings.

antipyretic, which pertains to its capacity to prevent fever. In contrast, Ibuprofen is categorised as a non-steroidal anti-inflammatory medicine, denoting its role in reducing inflammation. This combination effectively alleviates acute pain associated with several conditions, such as toothache and general body ache. The user has provided a numerical reference [3].

Overarching problems associated with FDCs that warrant attention and consideration:

- Due to variations in the pharmacokinetic profiles and half-lives of the different elements, concerns regarding FDCs include the possibility of changing the ideal dosage of one or more of the components.
- Since of the many medication profiles included in FDCs and since the pharmacogenetic profiles of individuals may vary during the production of FDCs, FDCs may further raise the risk of adverse drug responses or drug-drug interactions.
- Pharmacogenetic considerations are especially relevant to FDCs when the components represent either a crucial step in the commencement of action of the medicines of interest or an integral element of the main pathway for removing the medicines of interest.
- The pharmacokinetic characteristics of the elements of fixed-dose combinations (FDCs) are of significant importance in patients with infectious disorders, since the combination therapy may give rise to concerns regarding the development of resistance.
- Furthermore, it is crucial to take into account the pharmacokinetic and pharmacodynamic aspects of the elements when considering the senior population, as their safety profiles may be modified.
- Various studies have provided evidence indicating that the improper manufacturing of Fixed-Dose Combinations (FDCs) might lead to a decrease in their effectiveness or an increase in their toxicity when used in ordinary clinical practice. Additionally, these studies have highlighted that the peak effectiveness of FDCs may vary at different times, raising concerns about their shelf life.
- There are several additional concerns associated with Fixed-Dose Combinations (FDCs). One concern is the possibility of higher prices for FDCs compared to the combined cost of their individual components, unless there is a valid justification for the price difference. Another concern is that higher prices may be sustained through additional patent protection. Additionally, it can be challenging to determine which specific component of an FDC is responsible for any side effects that may occur. Lastly, there may be difficulties in adjusting the dosage of a specific ingredient, leading to patients receiving either insufficient or excessive amounts.
- In addition, fixed-dose combinations (FDCs) have the potential to contribute to an inaccurate diagnosis, particularly in cases of infections, and may result in reduced efficacy if patients fail to adhere to the prescribed regimen of the FDC, as compared to the individual components administered separately.

According to a gazette notification issued by The Central Government to ban a total of fourteen fixed-dose combination (FDC) drugs that have been considered to be absent of therapeutic value. As per the Central Drugs Standard Control Organisation (CDSCO), Fixed Dose Combinations (FDCs) are pharmaceutical preparations that are composed of one or more active components used for certain indications. The implementation of the prohibition, which has been enacted with immediate effect, aligns with the suggestions put out by a committee of experts that was established to evaluate the effectiveness of various combinations of drugs. The expert committee recommended that-

- There is no therapeutic justification for these FDCs and the FDCs may involve risk to human beings.
- In the larger public interest, it is necessary to prohibit the manufacture, sale or distribution" of these FDCs [4,5].

Advantages of fixed dose combination:

- Decrease in the number of pills required for treatment.
- The convenience in the process of dispensing.
- The topic of discussion pertains to the field of pharmaceutical management, specifically focusing on its simplicity.
- Enhances adherence and reduces default rate.
- The minimum level of prescription mistakes.
- There was a 50% decrease in the cost of therapy.
- The treatment strategy is straightforward and uncomplicated.
- There are various logistical advantages associated with the ordering, planning, and management of medications.
- Various components found in the Food and Drug Administration (FDA) approved combination (FDC) play a role in the collective therapeutic outcome.

- The majority of medications approved by the Food and Drug Administration (FDA) have demonstrated both safety and efficacy.
- Fixed-dose combinations (FDCs) are associated with reduced manufacturing and shipping expenses in comparison to the production costs incurred when making individual goods.
- The provision of affordable healthcare services, convenience, adherence to treatment protocols, and mitigation of the risk of antibiotic resistance are all ensured by this approach.
- FDC medications are employed in the treatment of various ailments and diseases, notably diabetes, HIV, malaria, and tuberculosis, which are widely recognised as significant global health challenges [3,6].

The drawbacks associated with FDCs:

The formulation of FDCs without proper due diligence gives rise to a number of connected difficulties-

- The pharmacodynamic mismatch between the two components occurs when one drug exhibits an additive or antagonistic action, resulting in decreased effectiveness or increased toxicity.
- Pharmacokinetic discrepancy and the occurrence of peak efficacy at varying time points.
- Chemical incompatibility resulting in a reduction in the duration of product stability.
- Drug interactions can occur due to the shared metabolic pathways.

While FDCs are extensively accessible across several treatment categories, a significant proportion of these combinations can be considered unusual. The therapeutic categories that exhibit a considerable quantity of fixed-dose combinations (FDCs) include preparations for cough, cold, and fever; analgesics and muscle relaxants; antimicrobials; medications for hypertension, dyslipidemia, diabetes, and psychiatric disorders along with vitamins and minerals. The FDC formulation may contain a varying number of components, perhaps more than five, regardless of the reason for their addition or the quantity used.

- Because the side effects of the mixed product in an FDC are different from those of its individual ingredients, it might not be safe to eat or drink.
- Putting two or more things together can sometimes cause risks that weren't there in the separate parts.
- When a patient has an adverse reaction, it's hard to figure out which ingredient caused the response.
- Many studies have shown that many of these mixtures are not better than taking the drugs separately.
- Antibiotic resistance has grown very quickly in India because of the widespread use of FDCs.
- The "ciprofloxacin-resistant – *Salmonella typhi* strains" example has made it hard and expensive to treat typhoid.
- Because of high demand and low production costs, drug businesses make a lot of money.
- If someone takes an FDC and has a bad reaction to it, it might be hard to figure out which active ingredient caused the response. This issue might be solved by starting each drug on its own and watching for side effects. If no issues are seen, the medicine can be switched to an FDC.

The prohibition of Fixed Dose Combinations (FDCs) in India:

- The patient may not require such a high number of medications, resulting in the potential for increased exposure to adverse effects.
- Individualization of medicine doses is necessary, taking into consideration factors such as patient health, medical history, age, and sex.
- Several firms in India have been marketing Fixed Dose Combinations (FDCs) without seeking approval from the central government. An example of such an FDC is the combination of cefixime and azithromycin, which has already been prohibited in the country.
- The inclusion of these non-essential FDCs has been shown to have detrimental effects [3,8,10].

CONCLUSION:

Although FDCs have many benefits, it is impossible to overlook their drawbacks. FDCs are being produced by pharmaceutical firms due to increased demand from consumers and prescribers. When discussing FDCs, factors such as drug-drug interactions, side effects, the lack of a need for other components when a single medication is required, difficulty identifying the drug component in the FDC when toxicity arises, etc. should be taken into account. The central government occasionally prohibits a large number of FDCs through the gazette after consulting with experts and recommending changes. In reality, this isn't happening, despite the fact that an FDC should be thoroughly examined before going on sale. These medications are synthetic, derived from chemicals, and every chemical

has certain physical and chemical characteristics. Any addition will undoubtedly change some or all of these characteristics. When one medication is added to another, the indications, contraindications, side effects, dose, mode of action, duration of action, etc. for each can vary. Because it involves health and life, a methodical and accurate analysis is necessary.

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