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RATIONALITY OF FIXED DOSE COMBINATIONS: AN INDIAN SCENARIO

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ABSTRACT

India is the country with significant drug use problems. There is concern regarding the irrational production, prescription and use of fixed dose combinations.The rationality of a fixed dose combination is the most controversial and debated issue in today's clinical practice. The Indian laws have not been properly defined to grant marketing approvals of the fixed dose combinations (FDCs) by state or central drug controlling authorities. Therefore, the state drug controlling authorities have continuously been approving various FDCs lacking any pharmacodynamic or pharmacokinetic advantages and acceptable rationale. Such type of approval without any preclinical and clinical studies leads to marketing of prescription-based irrational combinations.
Unfortunately, there seems to be no uniform worldwide acceptable criteria to define irrational FDCs and currently there are no uniform principles, guidelines or international standards addressing their development and regulatory assessment. Only a few countries have specific regulatory guidelines in place and so irrational combinations are still unbridled in several markets. Pharma industry is a major sponsor of scientific conferences and symposia in which information to doctors often emphasizes only the positive aspects of products and over looks or gives little coverage to the negative aspects. Such information about drugs and drug promotion can greatly influence the way in which drugs are used. Here is an attempt to critically review the serious Indian Scenario of fixed dose combinations prescribed widely.

Keywords: Fixed Dose Combination, Rationality

1. INTRODUCTION

The rational use of drugs requires that patients receive medicines appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and the community.

In an effort to initiate rational drug therapy, the World Health Organization (WHO) introduced the concept of an essential drugs list in 1977 and it updates the model list every two years. Subsequently after two decades in India, the Delhi Society for Promotion of Rational Use of Drugs (DSPRUD) was formed to promote the rational use of drugs. The 15th list of essential medicines by WHO has only about 25 FDCs.Although various opinions have been expressed regarding the rationality of FDCs, there are only a few

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studies taken up to find the rationality of FDCs [1].

Fixed dose combination [FDC] are highly popular in the Indian pharmaceutical market and are particularly flourishing in the last few years. The pharmaceutical industry has been manufacturing and marketing fixed dose combinations (FDCs), many of them irrational and harmful for the last two decades.

Initially not many in number, today they are in several thousands and a large number of them have no therapeutic rationale. The uncontrolled growth of such combinations in India more often than not has been the brainwave of marketing heads of pharmaceutical companies. Responding to the pressure for newer products, marketing heads of pharma companies used to invent combinations of two or more drugs, often launched without an assessment of their therapeutic benefits.

The most imperative concern with irrational FDCs is that they expose patients to unnecessary risk of adverse drug reactions. For instance, pediatric formulations of Nimesulide + Paracetamol can induce severe hypothermia in small children and lead to shock. FDCs of Diclofenac + Serratiopeptidase do not offer any particular advantage over the individual drugs despite vigorous claims that Serratiopeptidase promotes more rapid resolution of inflammation. On the other hand, the patient is exposed to greater risk of gastrointestinal [GI] irritation and serious bleeding from unsuspected peptic ulceration. FDCs of quinolones and nitroimidazoles (e.g. Norfloxacin + Metronidazole, Ciprofloxacin + Tinidazole, Ofloxacin + Ornidazole) have not been recommended in any standard books, but continue to be heavily prescribed drugs in GI infections, pelvic inflammatory disease, dental infections, etc., to cover up for diagnostic imprecision and the lack of access to laboratory facilities. Such injudicious use of antibiotic FDCs can rapidly give rise to resistant strains of organisms, which is a matter of serious concern to the health care situation in our resource-poor country [2].

2. DRUG CATEGORIES OF FDCs PRESCRIBED IN INDIA

Kastury N et al., (1999) reported that out of the total 300 prescriptions collected 225 contained FDC formulations. They were further sorted out as prescriptions containing one, two, three and four FDCs. These were 90 (30%), 93 (31%), 39 (13%), 3(1%), respectively. Out of these 225 prescriptions only 45 (20%) contained FDCs as recommended by the WHO in its list of essential drugs. In 10.2% of the FDC containing prescription, one ingredient was present at least two times both as a part of FDC formulation and as a single drug. Out of these 45(11%) FDCs were in accordance with recommended WHO list of FDCs. The most commonly prescribed were antimicrobials (15.55%), analgesics (15.8%), multivitamins (13.8%), antihypertensive (8.88%), and cough and cold remedies (8.64%), antidiarrhoeal (6.17%), antiasthmatic (3.70%) and others (16.3%). Drug categories of FDCs prescribed in India [3]. (Shown in figure 1).

3. CURRENT ISSUES ON IRRATIONALITY OF FDCs IN INDIA:

WHO model list of the essential medicines (March 2005) contains only 18 approved drug combinations (shown in table 1); whereas in India, there are so many FDCs (shown in table 2) being marketed in India but not approved in any developed country. Most of these combinations are not approved by the Drugs Controller General, India and hence illegal. (Source: CIMS, 2006)

The combination analgesics are extremely popular. There is a little evidence that any analgesic combination is better than its individual components alone. However, many patients are benefited with combination

probably because individual component may not have complete anti-inflammatory, analgesic and antipyretic activity.

Figure 1 Drug categories of FDCs prescribed in India (1999)

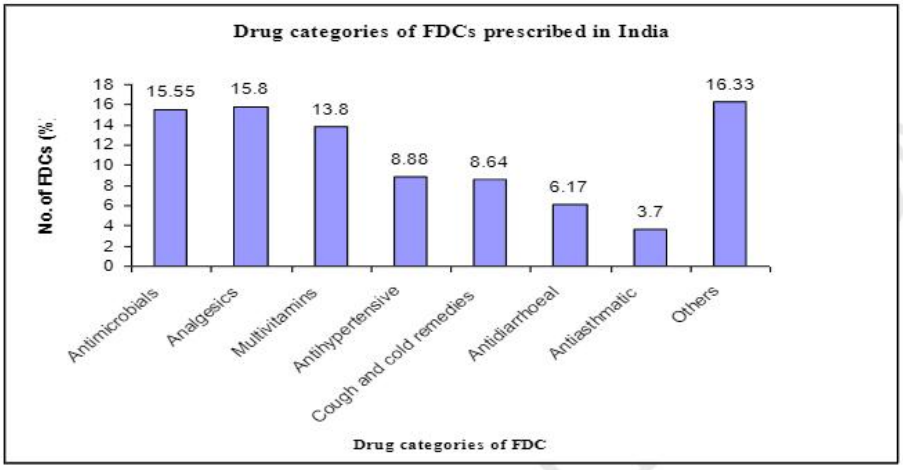

Table 1 Fixed-dose combinations in WHO's essential drugs model list

S.NO.	Fixed Dose Combination
1.	***Neomycin + Bacitracin (O)***
2.	***Amoxicillin + Clavulanic acid (T)***
3.	***Imipenem + Cilastatin (I)***
4.	***Sulfamethoxazole + Trimethoprim (T)***
5.	***Sulfamethoxazole + Trimethoprim (I)***
6.	***Isoniazid + Ethambutol (T)***
7.	***Rifampicin + Isoniazid (T)***
8.	***Rifampicin+Isoniazid+Pyrazinamide(T)***
9.	***Thiacetazone + Isoniazid (T)***
10.	***Benzoic acid + Salicylic acid (O)***
11.	***Ethinylestradiol + Levonorgestrel (O)***
12.	***Ethinylestradiol + Norethisterone(T)***
13.	***Ethinylestradiol + Levonorgestrel (T)***
14.	***Levodopa + Carbidopa (T)***
15.	***Ferrous salt + Folic acid (T)***
16.	***Sulfadoxine + Pyrimethamine (T)***
17.	Lidocaine + Epinephrine (I)
18.	***Oral Rehydration Salts: (P)***

O = Ointement, T = Tablet, I = Injection, P = Powder

In India, a variety of NSAID combinations are available, often as over-the-counter products. These combinations are the easiest way of selling two drugs when one (or even none) may be needed for the patient. These combination pills have now become the largest selling 'brands' of anti-inflammatory/analgesic/antipyretic products .There is no synergism when two drugs acting on the same enzyme are combined. Thus combining two NSAIDs or NSAID with analgesics like Paracetamol does not and cannot improve the efficacy or potency of treatment. If at all, it only adds to the cost of therapy and more important, to the adverse effects. Another most widely prescribed FDC's not having any rational basis is the multivitamin combinations and cough and cold remedies. WHO has deleted the combination of vitamins from its list with the comment that vitamins are considered part of nutrition and vitamin combinations should not be used indiscriminately. The cough mixtures contain expectorants; cough suppressants, antihistamine-mines, sympathomimetics, alcohol and other CNS depressants without any rational basis [4].

Table 2 List of some irrational fixed dose combinations

S.No.	Irrational FDCs	S.No.	Irrational FDCs
1.	Alprazolam + Imipramine	20	Alprazolam + Sertraline
2	Alprazolam + Melatonin	21	Alprazolam + Fluoexetine
3	Risperidone + Trihexyphenidyl	22	Imipramine + Diazepam
4	Norfloxacin + Tinidazole +Dicyclomine	23	Norfloxacin + Tinidazole
5	Norfloxacin + Metronidazole	24	Norfloxacin + Tinidazole +Loperamide
6	Ciprofloxacin + Tinidazole	25	Norfloxacin + Ornidazole
7	Ofloxacin + Tinidazole	26	Ciprofloxacin + Metronidazole
8	Ofloxacin + Ornidazole	27	Ofloxacin + Metronidazole
9	Doxycycline + Tinidazole	28	Fluconazole + Tinidazole
10	Mefenamic acid + Drotaverine	29	Tetracycline + Metronidazole
11	Nimesulide + Diclofenac	30	Nimesulide + Paracetamol
12	Nimesulide + Chlorzoxazone	31	Nimesulide + Dicyclomine
13	Nimesulide + Camylofin	32	Nimesulide + Methocarbamol
14	Nimesulide + Tizanidine	33	Nimesulide + Serratiopeptidase
15	Nimesulide + Tizanidine + Paracetamol	34	Nimesulide + Paracetamol + Chlorzoxazone
16	Ibuprofen + Tizanidine	35	Rofecoxib + Tizanidine
17	Diclofenac + Famotidine	36	Diclofenac + Tizanidine
18	Diclofenac + Serratiopeptidase	37	Diclofenac + Paracetamol + Tizanidine
19	Ibuprofen + Paracetamol + Magnesium Trisilicate	38	Diclofenac + Paracetamol + Serratiopeptidase

The Drug Controller General of India (DCGI) controversial order to withdraw 1105 combination drugs from the market seems to have lost transit. The order has not reached the drug controllers so far. The verbal order the drug controllers are in a dilemma to implement the directions which is giving the manufacturers helpless nights. Although the decision against the irrational combinations have been taken a month before ago, the state government are yet to receive the same. The decision to withdraw the combinations from the market was taken at the consultative committee meeting of state drug controllers convened last month in Delhi by the DCGI [**5**].

Approvals for most of the thousand of irrational combination drugs, currently in circulation in the country, were understood to have been first issued by the northern states where drug administration are generally weak with no competent officials to scrutinize such applications, it is learnt. Once the product licenses are obtained from these badly administered states, the pharmaceutical companies are free for market these products throughout the country. These irrational combinations are freely available in states such as Maharastra, Gujarat and Andhra Pradesh which usually disallows applications for such irrational combinations. As the combinations drugs have been in the market for some years and are doing well, the drug controllers in these states take a lenient view in giving the product licensed for manufacturing in these states also [6].

The Drug Controller General of India (DCGI) is learnt to be under the tremendous pressure from the pharmaceutical companies on withdrawal of irrational combinations drugs from the market as it affects a large number of drug units. Even after two months of his directive to the state Drug Controllers to withdraw licenses of irrational combinations, the Drug Controller General of India is to send the order of writing. Though the DCGI is the final authority to issue manufacturing licenses for all the new drugs, the state drug controllers are also empowered to issue licenses for combination of approve drugs. Often misusing the power, state drug controllers during the last ten years have issued manufacturing and marketing licenses for thousands of combination drugs [7].

The drug controller general of India is understood to be framing a broad policy document on fixed combinations to have an amicable way to settle the issue of weeding out irrational combinations from the market. The drive to clean up the market of irrational combinations has rattled the pharmaceutical industry. The directive to withdraw the listed combinations drugs, which were not so far cleared by the national authority, placed the pharma firms on the conclusions with court stays and loud protests. According to highly placed sources, the DCGI is working on the document and it would clear the grey areas on the vexed issue to help the companies and the state authorities. In October, the DGCI moved where states feared to tread. On October 26, the DGCI met state drug controllers and industry representatives the next day in Chandigarh. A list of 294 combinations was prepared and classified into different categories based on their irrationality and absurdity with the help of 100 pharmacologists [8].

The Drug Controller General of India (DCGI) has directed the state drug controllers to follow a strategy farmed by him in weeding out irrational drugs from the market. The DCGI has also directed the state drug controllers not to give manufacturing licences henceforth to FDC drugs without the approval

of the DCGI office in Delhi. With the help of the Pharmacologists, the DCGI has divided the 294 FDCs in question broadly into three categories. The first category is consisting of 120 combinations which are classified as banned, absurd and rejected. They are 16 absurd, 15 banned and 89 rejected. In the second category, there are 150 which need further examination. In the remaining 24 cases, five combinations are already approved whereas the rest require submission of clinical trial data, BE study and expert opinion. In the first phase, the DCGI has asked the state drug controllers to withdraw all combination drugs in the absurd, banned and rejected categories from the retail, wholesale and C&F agents immediately. There has been no disagreement on this from the industry representatives. In the second phase, the DCGI has directed the state drug controllers to withdraw the drugs in the 150 under observation category from the wholesalers and C& F agents. Industry has taken strong objection to the DCGI direction in the case of 150 FDCs which are under examination. The industry is of the view that since these drugs are under examination only and no adverse reactions are established at present, these drugs should be allowed to be manufactured and distributed [9].

By his own admission, the DCGI is on record saying that the DCGI office will come out with a result on the 150 combinations under examination in around 40 days. The industry has asked the DCGI to allow the drug units to manufacture these products till the DCGI comes out with his decision on these items. Stopping production immediately will result in huge financial loss to the companies, industry sources said. The industry associations will be meeting shortly to decide further course of action as the stand on DCGI on withdrawal is very clear. In the meeting with the industry representatives subsequently, the DCGI asked them to stop manufacturing all the 294 drug combinations forthwith.

4. CURRENT ISSUES ON IRRATIONALITY OF FDCs WORLDWIDE

Despite major advances in assuring the quality of FDCs, sub-standard and counterfeit FDC products circulate in the market.[10] Tenders for TB drugs to national TB control programmes often have limited emphasis on quality, and sometimes the buyers don't even require proof of bioavailability. The use of poor-quality drugs for TB treatment is dangerous, can lead to the death of patients and the creation of drug resistance, and must therefore be prevented. Among the range of necessary procedures for comprehensive quality assurance of any pharmaceutical product, [11, 12] bioavailability testing remains an important issue for assessing the quality of FDCs.

In the WHO Technical Report "Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability" [13] It is clearly stated that, "Where a drug produces meaningful concentrations in an accessible biological fluid, such as plasma, bioequivalence studies are preferred".

Taking an example of bioavailability of rifampicin proven bioavailability of rifampicin is an absolute requirement for the use of 4FDCs [14] (have four drugs present in a fixed ratio) Every FDC product in clinical use should be tested, and only those which pass should be allowed to be used. HPLC-based determination of rifampicin serum/plasma concentrations in 24 healthy volunteers, in whom up to 15 blood samples are collected over a period of 24-48 hours is regarded as the gold standard in assessing drug bioavailability. However, plasma-HPLC is expensive, cumbersome and time consuming, because it requires hospitalization of study subjects, close observation to ensure 100% compliance with the study protocol, and a large team to carry out drug administration,

blood taking and recording of each action at absolutely precise times. Also, the laboratory procedures are sophisticated and costly. To reduce costs, an abbreviated study protocol for bioavailability assessment of rifampicin was suggested, in which only six blood samples would be collected over an 8-hour period, and this abbreviated protocol showed closely similar results to those obtained using the extended protocol. However, even using the abbreviated protocol, serum/plasma based bioavailability testing remains largely impractical as a screening tool in drug procurement, particularly due to cost considerations.

A Pharmacopoeial monograph for the 4FDCs has been called to facilitate the quality assurance of these products. A monograph for the WHO-recommended 3FDC is available from United States Pharmacopeia (USP). Currently, there is no official monograph for the 4FDC published in internationally recognized pharmacopoeias, such as USP, British Pharmacopoeia (BP) and the International Pharmacopoeia. However, a draft version of a 4FDC monograph from USP is circulating for review and comments [15].

5. COMPRESSIVE CRITERIA FOR THE ASSESSMENT OF FDCs FOR RATIONALITY

Irrational use of medicines is a major problem worldwide due to this reason there must be some international standards and guidelines for the assessment of rationality of FDCs.

At this crucial juncture, when the global community represented by WHO is making an all out effort to propagate the concept of essential drugs amongst consumers throughout the world, our official stance could be viewed as too paltry. India being the world's second most populous country we should expect much more of ourselves and not pay mere lip service to the global campaign.

Irrational FDCs also impose unnecessary financial burden on consumers. Medical practitioners who patronize such combinations could be the center of controversy when subjected to litigation in consumer forums, as these combinations do not find mention in standard text or reference books and reputed medical journals.

The study of pharmacokinetic is an important component of both the research and development phases in the discovery of new drugs [16]. In research, chemical compounds will be screened in various biochemical and pharmacological tests to find compounds which show a positive effect. However, *in vitro* potency is not the only factor required by a good drug because many compounds which are potent *in vitro* are inactive *in vivo*. It is critically important that pharmacokinetic properties are given just as much weight as efficacy. Good efficacy but poor PK is unlikely to lead to a successful medicine, and failure during the development phase due to inappropriate PK is both expensive and inefficient [17].

Pharmaceutical manufacturers, releasing their combination products on the basis of *In Vitro* dissolution profile, according to USFDA guidelines, when both test and reference products dissolve 85% or more of the label amount of the drug in 15min, dissolution profiles may be accepted as similar without further mathematical evaluation [18,19]. Hence based on this, dissolution profiles or in-vitro bioavailability studies of FDC can be considered similar. Dissolution testing is one of the most widely used in vitro procedures in quality control of drugs [20, 21]. It is relatively cheaper and less labour-intensive than other procedures, but can`t be used reliable predictor of bioavailability. Therefore, evaluation of FDCs required well designed pre-clinical and clinical studies.

In medical science, bioavailability is considered to be a critical factor while administering a standard drug dosage form in patients [22]. The drug licensing authorities therefore have a responsibility to ensure that

every dosage form, allowed for manufacturing in the country, should have certain definite standards of bioequivalence of the drug originally approved by the DCGI. By granting manufacturing permission for formulation without bioequivalence study, the licensing officers are, thus exposing millions of patients in the country to the grave risk of irrational FDCs.

It is an accepted fact that an FDC be treated as a new drug, because by combining two or more drugs, the safety, efficacy, and bioavailability of the individual Active Pharmaceutical Ingredient (API) may change.

As per Rule 122B, D, E(C) (Appendix VI of Schedule Y) of the Drugs and Cosmetics Act of India, FDCs fall into four categories [24].

- The first group includes those in which one or more of the active ingredients are a new drug.
- The second group 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.
- The third group includes those which are already marketed, but in which it is proposed either to change the ratio of the active ingredients or to make a new therapeutic claim.
- The fourth group includes those whose active ingredients have been widely used in particular indication for years, their concomitant use is often necessary and no claim is proposed to be made other than convenience, and a stable acceptable dosage form, and the ingredients are unlikely to have significant interaction of a pharmacodynamic or pharmacokinetic nature.

  The groups (a)–(c) require adequate clinical data and the group (d) requires acceptable rationale that has to be submitted along with the application to get the marketing approval of FDC by DCGI, and not by individual state authorities. It may be of interest to mention that the model list of essential drugs prepared by WHO has only eighteen essential FDCs (WHO Technical Report, 2005), which would meet the medical needs of majority of the population. To develop comprehensive criteria which will be useful and unbiased for the evaluation of FDCs, the guidelines of WHO, "Note for guidance on fixed-dose combination medicinal products" by the Committee for Proprietary Medicinal Products (CPMP) Europe and several research papers were carefully studied. These are well-known guidelines, which serve as benchmark towards a rational FDC; based on these, the criteria for this study were developed. These criteria include all the dimensions of defining a rational FDC, and appropriate weighting (score) has been attached to each criterion[25].A Seven-point criteria for evaluating the rationality of FDCs has been established as follows [26-33]:

- API of the combination should preferably be in the essential medicine list (EML) of WHO or in the national list of essential medicines (NLEM) of India.
- Dose of each API should meet the requirements for a defined population group.
- Dose & proportion of each API present in FDC should be appropriate for intended use.
- Combination should have advantage of established evidence of efficacy &safety over single compounds administered separately in terms of its therapeutic efficacy and safety.

- Overall cost of the combination should preferably be less than the cost of the individual components.
- The FDC should facilitate either the reduction of the dose of individual drugs or their adverse effects.
- The PK properties of individual drugs should be similar.
- The PK parameters of each API should not be affected.
- There should be no unfavorable PK interaction between the APIs.
- Individual drugs should have different mechanism of action

6. CONCLUSION

Pharmaceutical manufacturers, however, continue to reap the benefits of huge sales, and therefore continue promoting them with vigor. Time has come for all of us, as practitioners and consumers, to raise this matter vociferously through all possible avenues. The campaign against meaningless FDCs must be carried on to every nook and corner of the country. The power vested in state-level drug regulatory authorities is often taken advantage of by pharmaceutical companies who push through irrational combinations without proper scrutiny. Therefore, in making this campaign a success we earnestly hope that our drug regulatory bodies would take urgent and stringent measures in mitigating such free flow of irrational FDCs.

Most of the drug control departments in the states and Union Territories in any case do not have the expertise or facilities to assess the merits and demerits of drug combinations. That amendment was observed more in the breach; state licensing authorities (SLAs) continued to permit FDCs over the years without insisting upon the statutory requirements of pre- clinical and clinical trials.

While combining two drugs, the efficacy and bioavailability of the two drugs undergo a change on account of the reactions between these chemicals. Therefore, detailed clinical trials and bioavailability studies have to be completed before such products are allowed to be marketed. For serious ailments such as TB and AIDS patients intake of more than one drug at a time for longer treatment period is critical and drug combinations are justified for the sake of patient compliance. It is far above the ground that pharmaceutical companies, healthcare professionals and regulatory authorities join hands and prescribe guidelines and international standard for the manufacturing and sale of FDCs.

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