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REGULATORY REASONS BEHIND THE BAN OF VARIOUS IRRATIONAL FIXED DOSE COMBINENT DRUGS

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Abstract:

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.

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INTRODUCTION [1-5]:

The Problems with Fixed Dose Combination:
The FDCs formulated without due diligence can pose problems namely (a) pharmacodynamic mismatch between the two components, one drug having additive/antagonistic effect leading to reduced efficacy or enhanced toxicity, (b) pharmacokinetic mismatch and having peak efficacy at different time, (c) chemical noncompatibility leading to decreased shelf life, (d) drug interactions because of the common metabolizing pathways, and (e) limitations of finer dosing titration of individual ingredients.

lthough FDCs are available in almost all therapeutic categories, many of them are bizarre combinations. The therapeutic categories having high number of FDCs are cough, cold, and fever preparations; analgesics and muscle relaxants; antimicrobials; drugs for hypertension, dyslipidemia, diabetes, and psychiatric disorders; and vitamins and minerals. The FDC formulation may have up to 5 or even more ingredients with or without rationality of their presence and in the quantity.

Very Few Fixed Dose Combinations in Essential List of Medicines [6-10]:

Essential medicines are those that satisfy the priority health care needs of the population and intended to be available at all times, in adequate amount and at 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 19th list of WHO List of Essential Medicines, 27 are FDCs. We included 24 FDCs out of 376 entities in the National List of Essential Medicines of India (NLEM) 2015. These FDCs were included after due deliberations in national consultations with scientific justifications. Majority of the FDCs in both the lists belong to antimalarial, antitubercular, antiretroviral drugs, which emphasize the importance of FDC use in treatment adherence and prevention of drug resistance.

Problem of Plenty: Fixed Dose Combinations with Questionable Justifications in India:

Notwithstanding with the basic principle of formulating FDC, the Indian medicine market has become the world leader of FDCs. The estimated number of FDCs in India is over 6000. Time and again, studies, editorials have shown violation of scientific merits in having many FDCs without adequate justification. Exploiting the liberal licensing system, many times, bizarre FDCs find place. India today does not have the exact database of currently available FDCs in the market, their sales turnover and use pattern. The existence of unlimited brands of FDCs with different permutations and combinations leads to confusion rather than guiding the prescribing doctor.

Fixed Dose Combinations are New Drugs but Permitted by State Licensing Authority: An Example of Disconnect:

As per the Rule 122E of Drugs and Cosmetics Act 1940, the FDCs are considered as New Drugs and the Central Drugs Standard Control Organization (CDSCO), after due examination of data on rationality, safety, and efficacy, issues approval. On the basis on this, the State Licensing Authority (SLA) gives the manufacturing and marketing permission. Incidentally, in the past, SLAs issued the license to manufacture and market without asking for no-objection from CDSCO. Thus, the efficacy, safety, and rationality of such FDCs remain questionable. This "disconnect" between the CDSCO and SLAs has precipitated a roadblock in the action against irrational FDCs.

Role of Strong Marketing and Key Opinion Leaders in Legitimizing Fixed Dose Combination:

The strong marketing pressure, inadequate time and attitude of critical analysis, influences the prescribing habit toward these FDCs. Senior leaders in medicine from academia and practice who are key opinion leaders influence the prescribing trend of their juniors and have a cascading effect on the medical community. Thus, frequent prescribing of FDCs and the near absence of adverse drug reaction reporting system in India legitimize this faulty practice. The high sales turnover and high prescription trend from Medical Colleges, Primary Health Centers, and general practitioners are often projected as their rationality, safety, and efficacy.

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; and 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 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.

The Regulatory Response to Proliferating Irrational Fixed Dose Combinations:

Many articles in print media and Nongovernmental Organizations questioned the rationality of FDCs. Drug regulator of India (CDSCO) came out with the policy guidelines for the approval of FDCs in 2013.[1] CDSCO has periodically banned various FDCs due to reasons such as lack of rationale or evidence and potential safety concern. In 2007, the Drugs Controller General of India (DCG [I]) issued edicts to all SLAs to withdraw 294 FDCs which were not approved by CDSCO. However, the industry disputed the ban and the matter is currently subjudice.[2]

The Parliamentary Standing Committee on Health and Family Welfare in its 59th report pointed out that some SLAs have been issuing manufacturing licenses for FDCs without prior clearance from DCG (I).[3] Subsequently, the DCG (I) issued a circular on January 15, 2013, directing the manufacturers to prove the safety and efficacy of FDCs licensed by the SLAs prior to October 1, 2012, within 18 months, failing which they would be considered for being prohibited from manufacture and marketing in India.[4] The FDCs approved before year 1988 were exempted. In response, 6220 applications were received from the industry.[2]

In September 16, 2014, Ministry of Health and Family Welfare (MOH and FW) constituted a committee for examining the applications for rationality, safety, and efficacy of the FDCs.[2] The committee submitted its report to the MOH and FW on April 16, 2015. It classified FDCs into 4 categories: (i) Category “a” – FDCs considered as irrational and the show-cause notices were issued to the manufacturers; (ii) Category “b” – FDCs requiring further deliberations with subject experts; (iii) Category “c” – FDCs considered as rational and letter of approval was sent; (iv) Category “d” – FDCs requiring further generation of data. Accordingly, letters were sent to submit phase four trial protocol to the manufacturers. Replies from manufacturers against show-cause notices with respect to 1083 irrational FDCs under category “a” were examined and the recommendations were submitted on February 10, 2016.[5] Based on findings of the expert panel, on March 10, 2016, 344 FDCs were prohibited under Section 26A of Drugs and Cosmetics Act, 1940.[6]

The industry moved the Hon’ble Delhi High Court seeking a stay on the ban notification citing the lack of regulatory power of the CDSCO to ban the manufacture of FDCs without revoking the license to manufacture given by the SLAs. Questions were raised on the procedure adopted by the DCG (I) such as not consulting Drugs Technical Advisory Board and Drugs Consultative Committee to decide on the prohibition.[7] The Government defended saying that the step of prohibition of the irrational FDCs was taken considering the public interest and the delay in administrative procedures in revoking the license.[8] A notification issued by DCGI on June 17, 2016, CDSCO has requested the concerned pharmaceutical manufacturers to furnish the Phase IV clinical trial protocol for the FDCs.[9] Despite all these, the original question of regulating and weeding out irrational the Bad FDCs and the Ugly FDCs is left in limbo among these technical and procedural convolutions.

What Interventions are Needed to Prevent Use of Irrational Fixed Dose Combinations:

To curb the irrational use of FDC in India, a multistep approach involving all stakeholders, for example, consumers, physicians, regulatory authority, industry, and the academicians, is needed. The enforcement mechanism by the regulators needs to be strengthened. Both the central and state regulators must harmonize their procedures for licensing FDCs. Good pharmacovigilance should be ensured to assess the performance of the product in clinical practice. Industry should act responsibly, ensuring the adequate rationale to develop FDC and generating robust efficacy and safety data. National Formulary of India, NLEM, and Standard Treatment Guidelines should be

adopted across different levels of health services. CMEs on drug information, training medical and pharmacy students with an orientation toward the public health implications of FDCs misuse and good prescribing and pharmacy practices will go a long way in addressing the knowledge, attitude, and practice gap of practicing physicians and pharmacists. A multipronged corrective approach involving regulator, academia, industry, physicians, and public is needed to correct the dismal FDC scenario in the country.

India's ban on antimicrobial fixed-dose combinations: winning the battle, losing the war [11-15]:

India, the country with the largest market availability of antimicrobial fixed-dose combinations (FDCs), banned certain antimicrobial FDCs in September 2018. Our objective was to examine the impact of Government ban on the sales of antimicrobial FDCs.

METHODS:

The sales patterns of 14 of the 26 banned antimicrobial FDCs were analyzed using monthly private sector drug sales data from IQVIA (a comprehensive and nationally representative drug sales database) between January 2018 and December 2019. We carried out descriptive analyses to evaluate the trend in sales over time for banned and non-banned antimicrobial FDCs using cumulative sales volumes.

RESULTS:

Overall, the cumulative sales volume of banned antimicrobial FDCs declined by 75% between January and September 2018 and the same months of 2019, although some banned FDCs continued to be available in significant volumes. The effectiveness of the ban was offset by several pathways. First, the sales of combinations containing moieties belonging to the same drug-classes as the antimicrobials in the banned FDCs increased after the ban. Second, while certain formulations of particular combinations were banned, the sales of other non-banned formulation of these combinations increased. Third, in some cases, products containing new non-antimicrobial components added to the banned combinations remained available.

Interpretation and conclusions:

While sales of the banned antimicrobial FDCs decreased in 2019, we identified several mechanisms that counterbalanced the ban, including implementation failure, rising sales of congeners, and products with additional non-antimicrobial components.

CONCLUSION:

In conclusion, while the reductions in sales of the banned FDCs show that legal actions can be partially successful, we observed an increase in sales of non-banned antimicrobial FDCs. Therefore, effective control of antimicrobial FDC consumption will need more carefully crafted regulatory and societal solutions.

REFERENCES:

1. Van Boeckel TP, Gandra S, Ashok A, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis.* 2014;14:742–750. doi: 10.1016/S1473-3099(14)70780-7. [PubMed] [CrossRef] [Google Scholar]
2. CDSCO. Report of Expert Committee on Fixed Dose Combinations (FDCs) Licensed by SLAs for Manufacture without Approval of DCG (I), Applications of Which Received by CDSCO. 2015. [Last accessed on 2016 Jun 18]. Available from: http://www.cdsco.nic.in/writereaddata/fdcexpert%2019.1.2016.pdf .
3. CDSCO. Department-Related Parliamentary Standing Committee on Health and Family Welfare Fifty-Ninth Report on the Functioning of the Central Drugs Standard Control Organization (CDSCO) 2012. [Last accessed on 2016 Jun 18]. Available from: http://www.164.100.47.5/newcommittee/reports/englishcommittees/committee%20on%20health%20and%20family%20welfare/59.pdf .
4. CDSCO. Letter Dated 15.01.2013 on Approval of Safety and Efficacy of Fixed Dose Combinations Permitted for Manufacture of Sale in the Country without Due Approval from DCGI. 2013. [Last accessed on 2016 Jun 18]. Available from: http://www.cdsco.nic.in/writereaddata/Approval_of_the_safety_and_efficacy_of_FDC.pdf .
5. CDSCO. Report of Expert Committee on Evaluation of Cases of Fixed Dose Combinations (FDCs) Considered as Irrational and Where Showcause Notices were Issued to the Applicants to Submit Their Replies. 2016. [Last accessed on 2016 Jun 18]. Available from: http://www.cdsco.nic.in/writereaddata/fdcreport10_2_2016.pdf .
6. CDSCO. Prohibition of Fixed Dose Combination Drugs for Human Use Under Section 26A of Drugs and Cosmetics Act, 1940. 2016. [Last accessed on 2016 Jun 18]. Available from: http://www.cdsco.nic.in/writereaddata/SKM_12-03-2016.pdf .
7. Raghavan P. ET Bureau (March 30, 2016). Delhi High Court Refuses to Vacate Stay on Drug Ban.

2016. [Last accessed on 2016 Jun 18]. Available from: http://www.articles.economictimes.indiatimes.com/2016-03-29/news/71900265_1_drugcontroller-general-delhi-high-court-central-drug-regulator .

8. Press Trust of India. (April 4, 2016). How Can Government Ban a Drug Without Cancelling Licence, Asks High Court. 2016. [Last accessed on 2016 Jun 18]. Available from: http://www.financialexpress.com/article/industry/companies/how-can-govtban-a-drug-without-cancelling-licence-asks-high-court/232560/
9. CDSCO. Notice Dated (June 17, 2015). Examination of Safety and Efficacy of FDCs Licensed for Manufacture for Sale in the Country without Due Approval from Office of DCGI. 2015. [Last accessed on 2016 Jun 18]. Available from: http://www.cdsco.nic.in/writereaddata/notice%20letter17_6_2016_2016.pdf .
10. Brahmaiah Bonthagarala, Current Regulatory Requirements for Registration of Medicines, Compilation and Submission of Dossier in Australian Therapeutic Goods Administration, International Journal of Advanced Scientific and Technical Research, ISSN 2249-9954, Issue 6 volume 6, November-December 2016, 144-157.
11. Brahmaiah Bonthagarala, Comparison of Regulatory Requirements for Generic Drugs Dossier Submission in United States and Canada, International Journal of Pharmaceutical Science and Health Care, ISSN 2249 – 5738, Issue 6, Vol. 6 (November-December 2016), 1-19.
12. Brahmaiah Bonthagarala, Nanomedicine Clinical Use, Regulatory and Toxicology Issues In Europe, Journal of Drug Delivery and Therapeutics, 2019; 9(4-s):846-848.
13. Brahmaiah Bonthagarala, A Review on global harmonization task force (GHTF) - principles of in vitro diagnostic (IVD) medical devices classification, The Pharma Innovation Journal 2018; 7(7): 667-672, ISSN (E): 2277- 7695.
14. Brahmaiah Bonthagarala, Compilation of Chemistry Manufacturing Controls In Abbreviated New Drug Application, Journal of Pharma Research, Vol-08, Issue 08, 2019.
15. Nayyar GML, Breman JG, Mackey TK, Clark JP, Hajjou M, Littrell M, et al. Falsified and substandard drugs: Stopping the pandemic. Am J Trop Med Hyg. 2019;100(5):1058–65.