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The proliferation of irrational metformin fixed-dose combinations in India

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India's pharmaceutical market, valued at more than US$12 billion in 2009 and projected to exceed $55 billion in 2020, is one of the largest markets in the world.[1] The Indian generics industry manufactures drugs for use all over India and is also a major exporter, especially to low-income countries with scarce local manufacturing capacity. The Indian regulatory body, Central Drugs Standard Control Organization (CDSCO), is required by law to ensure that drugs are safe and effective.[2]

In 2012, a scathing Indian Parliamentary report[3] indicated that CDSCO had "skewed priorities…according primacy to the propagation and facilitation of the drugs industry" and concluded that CDSCO had a blatant disregard for public health objectives. The report emphasised how new drug approvals were granted in the absence of evidence of efficacy and without the necessary clinical trials. In response to this report, the Drug Controller General of India established an expert committee, chaired by Ranjit Roy Chaudhury, to formulate regulatory policy, guidelines, and standard operating procedures for approval of all new drugs; in effect, to introduce a complete overhaul of the pharmaceutical regulatory system in India.[4] The 2013 Drug Controller General of India Expert Committee (Ranjit Roy Chaudhury Expert Committee) report noted that many of the 85 000 drug formulations available in India should not be marketed at all and recommended an urgent review of the scientific basis for their approval.[4] Of particular concern was the absence of progress on withdrawing current approvals for oral fixed-dose combinations (FDCs), which are a feature of the Indian pharmaceutical landscape.[2] In 2007, the Drug Controller General of India issued edicts to all states of India demanding market withdrawal and cessation of the manufacturing of 294 FDCs on the grounds that they were "banned, absurd, rejected, or under investigation"; but to little or no avail.[4] In 2012, the Ministry of Health and Family Welfare prohibited the manufacture and sale of 91 drugs, of which 45 are FDCs.[5]

Drugs for treating type 2 diabetes show the scale of the problem. CDSCO has approved 41 FDC formulations for type 2 diabetes that, in turn, have given rise to more than 500 marketed brands.[6] In some cases, drugs were launched prior to CDSCO giving approval (table). Type 2 diabetes is increasing in incidence, with an estimated 60 million people affected in India.[7] However, in view of the constant monitoring and rapid adjustment of treatment regimens required to maintain adequate glycaemic control, metformin FDCs are not recommended by international or national treatment guidelines for the management of type 2 diabetes.[8,9] Guidelines from the Indian Ministry of Health and Family Welfare, the Indian College of Physicians, and the Indian Council of Medical Research follow the current International Diabetes Foundation guidelines, which advocate using diet and exercise as a first-line treatment to control type 2 diabetes, with oral antidiabetic monotherapy started if necessary, and further treatment added only as needed to achieve glycaemic control.[10] Only metformin and glibenclamide monotherapies are listed on the Indian Essential Medicine List.[9] However, sales volumes of metformin FDCs outstrip metformin single-drug formulations by 3:1 and account for 56% of all oral antidiabetic drug sales in India (table; data obtained from PharmaTrac sales and volume data 2012).[11] From November, 2011, to October, 2012, the five top-selling metformin FDCs accounted for 87% of sales volume and 75% of monetary value of all metformin FDCs in India.[11]

	Pharmatrac Data (Nov 2011 – Oct 2012)			CDSCO[6]		Worldwide[11]
	Sales units	Sales value	Brands (manufacturers)	Market launch	Approval date	Availability in Australia[a] or USA[b] (approval date; number of brands available)**
Five top-selling metformin FDCs in India	397 100 000	15 099 000 000	365 (297)			No
glimepiride-metformin	158 800 000	7 437 000 000	137 (99)	Sept, 2002	Nov, 2002	No
glimepiride-pioglitazone-metformin	77 300 000	4 112 000 000	68 (55)	Dec, 2003	Dec, 2005	No
glipizide-metformin	68 400 000	564 000 000	25 (22)	Nov, 1998	March, 1998	Yes[b] (2002; 7)
glibenclamide*-metformin	48 800 000	978 000 000	33 (32)	Aug, 2001	Nov, 1995	Yes[a] (2004; 2) Yes[b] (2000; 7)
gliclazide-metformin	43 800 000	2 008 000 000	102 (89)	Nov, 1999	April, 2005	No
All diabetes FDCs (% of which are the five top-selling metformin FDCs)	457 900 000 (86·7%)	20 250 000 000 (74·6%)	569	..	..	..
All metformin SDFs	148 000 000	2 673 000 000	123	..	..	..
All metformin FDCs	455 400 000	20 115 000 000	536	..	..	..
All metformin SDFs and FDCs (% which of are the five top-selling metformin FDCs)	603 400 000 (65·8%)	22 788 000 000 (66·3%)	659	..	..	..

FCDs=fixed-dose combinations. SDFs=single-dose formulations.* Known as glyburide in the USA. ** None of the listed FDCs are presently available in the UK.

Table: **FDCs and SDFs used to treat type 2 diabetes in India**

Although 41 metformin FDCs have been approved for the treatment of type 2 diabetes in India, CDSCO does not publish the justification for new drug approvals. Moreover, the Indian clinical trials registry, mandatory only since 2009, has no data on the results of antidiabetic FDC drug trials conducted in India.[12] Most metformin FDCs sold in India have not been shown to be safe and effective for the treatment of diabetes, and there are few clinical trials with Indian patients. For example, for the top-selling metformin FDC in India (a combination of glimepiride and metformin), only three of the 15 trials we identified had been published, and only one of these trials involved Indian patients (appendix). In the absence of a Cochrane Review, the only two systematic reviews on oral medications for type 2 diabetes have no trial data comparing treatment outcomes using FDCs with those of the component medications used concomitantly as single-drug formulations (appendix). None of the metformin FDC trials meet WHO guidelines for approval of FDCs and recommended criteria for efficacy and safety.[13] With such large volumes of metformin FDCs in the Indian market, this inadequate control is deeply worrying.[11]

In November, 2013, the Drug Controller General of India Expert Committee published a further report noting that there had been little governmental progress in the implementation of its earlier recommendations and that irrational and potentially dangerous drugs were still widely available in the Indian market.[14] The reasons for lax approval processes and the clinical rationale underpinning the proliferation of irrational FDCs in India—including evasion of price controls for essential medicines, marketing strategies of industry, attitudes of prescribers and patients, and the ability of states to override national law—needs to be better understood. The India Drug Act makes it possible for companies to evade CDSCO approval for FDCs due to the different responsibilities that exist and tensions that arise between state drug controllers and the federal Government; a new Act is long overdue.[2]

Until a new Act is declared, in the interest of public health, the recommendations of the Drug Controller General of India Expert Committee would be more easily implemented if CDSCO were to publicise the evidence for metformin FDC approvals and the basis for determining efficacy and safety. CDSCO should also consider taking steps to withdraw licenses for metformin FDCs until the manufacturers make this evidence publicly available. The Drug Controller General of India Expert Committee has made it quite clear that it expects CDSCO to strictly adhere to the highest standards of safety, quality, and efficacy for all FDC products and that these public health objectives are both necessary and compatible with the Indian pharmaceutical industry's dominant role in international markets.

See Online for appendix

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