

Adequacy of clinical trial evidence of fixed-dose combinations for the treatment of type 2 diabetes mellitus in India

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ABSTRACT

There is growing national and international concern about the drug regulatory system in India. Parliamentary reports have highlighted the presence of high numbers of unapproved medicines and irrational combinations of both approved and unapproved drugs in the Indian marketplace. Fixed-dose combinations (FDCs) are a peculiar feature of the Indian pharmaceutical landscape. Although metformin is a first-line treatment, FDCs for diabetes in India account for two-thirds of all diabetes medicine sales, and some have not been approved by the Central Drugs Standard Control Organization (CDSCO). This study examines the basis of efficacy and safety of top-selling metformin FDCs in India against four WHO criteria from clinical trials guidelines for the approval of FDCs. Data from a commercial drug sales database (PharmaTrac) were combined with searches through published literature, clinical trial registries, and published and unpublished trial websites of metformin FDCs in adults with type 2 diabetes mellitus. Five metformin FDCs in India from November 2011 to October 2012 accounted for 80% of all metformin FDC sales by value and volume. Although all five had obtained CDSCO approval, three had been sold and marketed prior to receiving this approval. Evaluation of published and unpublished clinical trials of these five FDCs found none provided robust evidence of safety and efficacy for the treatment of type 2 diabetes. Recommendations are made for publishing evidence that underpins drug approvals, marketing bans, greater transparency through updated clinical trials databases and legislative reform in order to prevent irrational FDCs from entering the market.

INTRODUCTION

Clinical trials are a crucial step in the development of new medicines. They are required by national drug regulatory agencies to ensure medicines are safe and effective for use in a human population. Every country is responsible for maintaining a stringent system to control the distribution of medicines within their borders. Typically, this requires the successful completion and adequate presentation of results from phase I through phase III clinical trials, from preliminary safety data to the analysis of safety and efficacy results

Key questions

What is already known about this topic?

- ▶ Although metformin is a first-line treatment for diabetes, fixed-dose combinations (FDCs) in India account for the majority of diabetes medicine sales.
- ▶ The five top-selling FDCs account for 500 brands; multinational corporations manufacture all five FDCs.
- ▶ Different dosages of three of the five top-selling metformin FDCs were banned by the government in March 2016 in its ban of 344 irrational FDCs, but the ban was overturned by the Delhi High Court in December 2016. The government is challenging this in the Supreme Court of India.

What are the new findings?

- ▶ A review of both published and unpublished clinical trials for the five top-selling metformin FDCs in India found only one study evaluating the efficacy and safety of a metformin FDC versus concomitant use of the component drugs as single-drug formulations; it was underpowered and of poor quality.
- ▶ None of the 25 clinical trials for the five top-selling FDCs met all four selected criteria from WHO guidelines for the conduct of trials and approval of FDC medicines.

from extensive human trials. The US Food and Drug Administration (FDA) approves approximately 40 new medicines for the US market each year through this process.¹ Drug approval packages for new drugs, which include a full review of submitted materials for approved drugs, are available through the FDA's website. India approves more than 100 new medicines a year but does not publish data on submitted applications or summaries of approved medicines, and concerns have been raised about the safety and efficacy around medicine approvals in the absence of appropriate clinical trials.²⁻⁵



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Key questions

Recommendations for policy

- ▶ The safety and efficacy considered by the Central Drugs Standard Control Organization in approving the five top-selling metformin FDCs for the treatment of type 2 diabetes mellitus in India should be published immediately. If the evidence does not extend beyond the trials reviewed in this paper, those FDCs should be banned immediately. If that evidence includes the results of trials not reviewed in this paper, but those trials do not meet the WHO standards used here for evaluation, those FDCs should be banned.
- ▶ Clinical trial databases should be constantly updated with both protocols and outcomes in order to improve transparency of trial data; evidence underpinning drug approvals should be published.
- ▶ Legislation on clinical trial and data submission requirements for FDCs should be revised and aligned with WHO recommendations in order to prevent irrational FDCs from entering the market and to improve transparency.
- ▶ The government’s March 2016 ban on FDCs should be reinstated and a review of FDCs mandated by the Indian Parliament.

Over 60million people have been diagnosed with type 2 diabetes mellitus in India, which has been described as ‘the diabetes capital of the world’.⁶ Given the constant monitoring and rapid adjustment of treatment regimens required to maintain adequate glycaemic control, metformin fixed-dose combinations (FDCs) are not recommended by national or international treatment guidelines. Nevertheless, the Central Drugs Standard Control Organization (CDSCO), India’s drug regulator, has given approval for 52 FDC formulations for type 2 diabetes, which in turn has given rise to more than 500 marketed brands of metformin FDCs. In contrast, only two metformin FDCs are approved in the USA, one in Australia, and none in either the UK or Canada (figure 1).^{3 4} Twenty-seven metformin FDCs were included in the Indian government’s ban of 344 unapproved FDCs in March 2016 as having ‘no therapeutic justification’ following consideration of nearly 6000 unapproved FDCs by an expert committee (see online supplementary table 1).² The ban was lifted in December 2016

by the Delhi High Court, but an appeal to the Supreme Court is pending.⁷

One of the primary arguments for prescribing FDCs for treatment of type 2 diabetes is improved adherence to treatment due to convenience.^{8 9} While some studies suggest FDCs are associated with better adherence than concomitant single-drug formulations (SDFs), they should only be considered when the patient has been stable on a regimen of concomitant SDFs for an extended period of time.^{10–13} Glucose levels fluctuate and treatment adjustments are often needed, but such adjustments are particularly difficult when using FDCs because doses are fixed. Regardless, the convenience of FDCs should not trump efficacy.

The availability of irrational or inadequately tested medicines puts the safety of the public at risk. It is important to ensure that those medicines that are available on the market have been approved after examination for safety and efficacy through the implementation of appropriately designed and analysed clinical trials. This work is an evaluation of the clinical evidence on the safety and efficacy of the most common metformin FDCs sold for treating type 2 diabetes in India.

GATHERING THE LEGAL EVIDENCE

Indian rules

Drugs in India are regulated by the Drugs and Cosmetics Act 1940 and the Drugs and Cosmetics Rules 1945, both of which have been amended many times. Imports and marketing of new drugs are controlled nationally by CDSCO, while manufacture, distribution and sale of drugs are the responsibility of the States. ‘New drugs’ as a category of ‘drugs’ was first introduced into the Rules in 1952, and FDCs were expressly mentioned as a specific subcategory of new drugs in 1988. Part X-A and Schedule Y of the Rules—initially inserted in 1988 and significantly revised in 2005—set the requirements for manufacturing and importing new drugs, including FDCs, for the purposes of conducting clinical trials or marketing (table 1).¹⁴ CDSCO must give permission before manufacture and

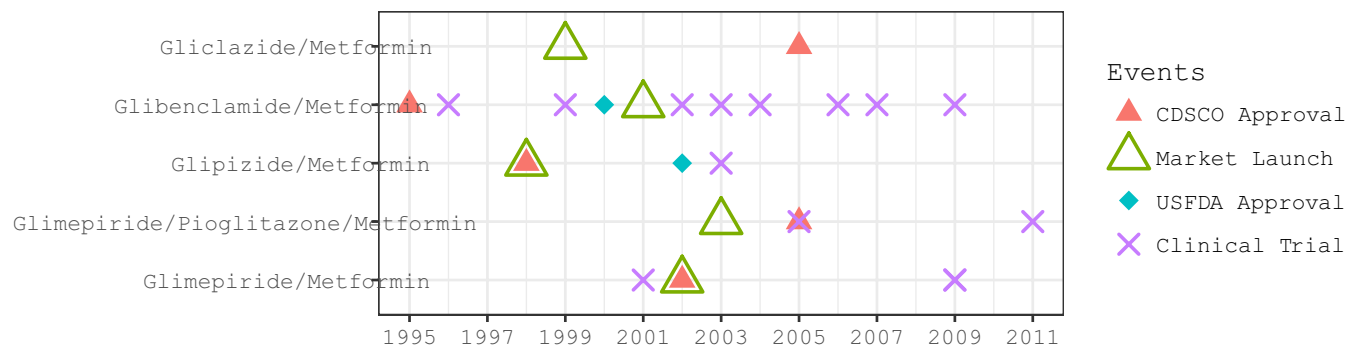


Figure 1 Timeline of important events concerning the five top-selling fixed-dose combinations in India. CDSCO, Central Drugs Standard Control Organization; US FDA, US Food and Drug Administration.

Table 1 Extracts from the opening paragraphs of Schedule Y in 1988 and in 2005, comparing the provisions on phase II, III and IV trials as they relate to numbers of trial subjects and centres¹⁴

Trial phase	1988 Schedule Y	2005 Schedule Y
Phase II	'Normally 10–12 patients should be studied at each dose level. These studies are usually limited to 3–4 centres...'	'Studies in Phase II should be conducted in a group of patients who are selected by relatively narrow criteria leading to a relatively homogeneous population. These studies should be closely monitored... If the application is for conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and the patients as well as the justification for undertaking such trials in India shall be provided to the Licensing Authority'.
Phase III	'If the drug is already approved/marketed in other countries, phase III data should generally be obtained on at least 100 patients distributed over 3–4 centres primarily to confirm the efficacy and safety of the drug in Indian patients when used as recommended in the product monograph for the claims made. If the drug is a new drug substance discovered in India, and not marketed in any other country, phase III data should be obtained on at least 500 patients distributed over 10–15 centres'.	'(iii) For new drugs approved outside India, Phase III studies need to be carried out primarily to generate evidence of efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information. Prior to conduct of Phase III studies in Indian subjects, Licensing Authority may require pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad. (iv) If the application is for the conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and patients as well as the justification for undertaking such trials in India should be provided to the Licensing Authority along with the application'.
Phase IV*	'In addition, data on adverse drug reactions observed during clinical use of the drug should be collected in 1000–2000 patients...'	'Post Marketing trials are studies (other than routine surveillance) performed after drug approval and related to the approved indication(s). These trials go beyond the prior demonstration of the drug's safety, efficacy and dose definition. These trials may not be considered necessary at the time of new drug approval but may be required by the Licensing Authority for optimising the drug's use. They may be of any type but should have valid scientific objectives. Phase IV trials include additional drug-drug interaction(s), dose-response or safety studies and trials designed to support use under the approved indication(s), for example, mortality/morbidity studies, epidemiological studies etc'.

*In 1988, phase IV trials were not specifically mentioned in Schedule Y: the 1988 text above is a continuation of the 1988 Schedule Y text for phase III trials.

import for these purposes. New drugs, including FDCs, cease to be considered 'new drugs'—and so no longer need CDSCO approval for marketing—4 years after their first approval. A duty on the regulator to be satisfied before approval that new drugs, including FDCs, are safe and effective was only imposed in 2001.¹⁵

Clinical trial requirements

Clinical trials must be carried out in India on 'new drug substances discovered in India' from phase I or from phase III if 'discovered' outside India. As shown in table 1, the 1988 rules specified the minimum numbers and ranges for trial participants and sites, but these were amended and downgraded in 2005.¹⁴

FDC data submission requirements

The data submission requirements for an FDC depend on which one of four FDC categories in Appendix VI of Schedule Y the FDC in question falls into: (1) one or more of the active ingredients is a new drug; (2) active

ingredients already approved or marketed individually are combined for the first time; (3) already marketed but a change in active ingredient ratios is made; and (4) active ingredients concomitantly have been used for a particular indication for an extended period of time (a claim of convenience).¹⁴ These requirements and categories have been analysed previously, highlighting poor drafting and the downgrading of the rules in 2005.¹⁵

It is impossible to know what clinical evidence is before the regulator when it decides to approve an FDC for marketing for three reasons. First, although CDSCO publishes a list of FDCs that have been given marketing approval, no information is publicly available on which FDC category any particular approved FDC falls, and therefore the data submission requirements applying to a specific FDC are unknown.¹⁶ Second, CDSCO can override data submission requirements. It has a wide power to dispense with the requirement to submit data 'if satisfied that there is adequate published evidence regarding

the safety of the drug'. In 2005, a further discretion was added, allowing toxicological and clinical data requirements to be 'abbreviated, deferred or omitted' if the drugs addressed 'life threatening/serious diseases or diseases of special relevance to the Indian health scenario'. The Rules are silent on what constitutes the public interest, adequate published safety evidence and on what diseases are covered. The Rules do not require CDSCO to explain or make public its reasoning when exercising these discretions, and no public information is systematically made available as to whether they have exercised them. Third, the regulator does not publish or summarise the clinical evidence submitted to it or its evaluation of that evidence.

Guidance from CDSCO

There appears to be no finalised guidance on FDCs published by CDSCO.

Its website contains a draft document entitled 'Guidance for Industry on Fixed Dose Combinations', dated April 2010, 'for feedback purposes only. Comments and suggestions regarding this draft document should be submitted within 30 days of publication'.¹⁷ The document focuses on the forms and payments that drug companies must use and make and contain little substantive guidance beyond reiterating the rules, and do not use the same FDC categories as those set out in Appendix VI of Schedule Y.¹⁴ The CDSCO website also contains a document entitled 'System of preliminary scrutiny by CDSCO at the time of receipt of application for approval of Fixed Dose Combinations', which is stated to be effective from 1 January 2011 but contains little substantive content.¹⁸

WHO guidelines

In 2005, the WHO adopted its guidelines for registration of fixed-dose medicinal products 'intended to provide advice to those countries that do not, as yet, have guidelines for this type of product' (see online supplementary figure 1).¹⁹ While India has had FDC-specific rules since 1988, as well as draft industry guidance and a preliminary scrutiny document, the WHO guidelines are more extensive, substantive and clearly drafted. They contain a set of 'general principles' applying to clinical efficacy and safety evidence and assessment, which do not appear in the Indian Rules or administrative documents.

GATHERING THE CLINICAL TRIALS EVIDENCE

We previously reported PharmaTrac data of the five top-selling metformin FDCs in India for the 12-month period of November 2011 to October 2012.^{4 20} The following were the resulting five top-selling metformin FDCs: (1) glimepiride/metformin, (2) glimepiride/pioglitazone/metformin, (3) glipizide/metformin, (4) glibenclamide/metformin, and (5) gliclazide/metformin. Although all five of these top-selling formulations were approved by CDSCO, three of these, glimepiride/metformin, glimepiride/pioglitazone/metformin and gliclazide/metformin, were launched on

the market prior to CDSCO approval (figure 1).⁴ PubMed and Embase databases and the Cochrane Library were searched from 1 January 1980 to 1 April 2016 for all published clinical trials on patients with type 2 diabetes investigating the five top-selling FDCs (see online supplementary figures 2 and 3). After application of inclusion/exclusion criteria, 25 publications remained eligible for inclusion: 3 of glimepiride/metformin, 2 of glimepiride/pioglitazone/metformin, 1 of glipizide/metformin, 19 of glibenclamide/metformin and none of gliclazide/metformin (online supplementary figures 4 and 5 and tables 2, 3 and 4 illustrate the results of the search strategy for unpublished trials and detail the 16 retrieved unpublished trials).

Overall, 23 of the 29 separate comparator arms (from 25 trials) examined glibenclamide/metformin; three, glimepiride/metformin; two, glimepiride/pioglitazone/metformin; one, glipizide/metformin; none, gliclazide/metformin. In order to assist in the analysis, we grouped them into six categories of comparator arms: (1) FDC versus concomitant treatment with the FDC components given as SDFs; (2) FDC versus monotherapy with one of the components; (3) FDC versus a different FDC combination or concomitant SDF diabetes treatment; (4) FDC versus FDC with the same components but comparing different dosages or formulations (ie, dose 1 vs dose 2); (5) other (eg, same FDC in the same dosage/formulation but under fed versus fasting conditions or no comparator); and (6) new FDC formulation versus previously marketed FDC (table 2). Only one trial compared an FDC (glibenclamide/metformin) versus concomitant treatment with glibenclamide and metformin.²¹ It was a 2-week trial in 40 patients by an MNC, which evaluated glucose levels (not haemoglobin A1c (HbA1c)) but not adverse events. The trial was inadequately powered and was too short to support a robust evaluation of efficacy or safety of the FDC.

Only three clinical trials of metformin FDCs on patients with type 2 diabetes were conducted in India. One was a trial of 28 patients of 3-month duration and two other trials included 101 patients comparing the FDC glimepiride/pioglitazone/metformin with metformin plus insulin or no treatment.²²⁻²⁴

WEIGHING THE CLINICAL TRIALS EVIDENCE

Because CDSCO's rules governing the approval of FDCs in India provide a great deal of latitude and have been weakened over time, we used the WHO's 2005 Technical Report, *Guidelines for Registration of Fixed-Dose Combination Medicinal Products*, which was intended to provide guidance to drug regulatory agencies on robust registration requirements for FDCs given their growing use in treating diseases such as HIV, malaria and tuberculosis (see online supplementary figure 1).¹⁹ On the basis that diabetes is highly prevalent in India and affects millions of people, treatment is long term, and risks of hypoglycaemia and poor tolerance are well-reported, we adopted

Table 2 Categories of comparator arms in 42 published and unpublished clinical trials of metformin FDCs in patients with type 2 diabetes.

Metformin FDC	Published/ Unpublished	Categories of comparator arms					Experimental vs marketed**
		FDC vs concomitant SDFs*	FDC vs monotherapy†	FDC vs other‡	FDC vs FDC§	Other¶	
Glimepiride CDSCO approval 2002	Published	0	1	2	0	0	0
	Unpublished	0	5	1††	3††	3	1
Glimepiride/Pioglitazone CDSCO approval 2005	Published	0	0	1	0	1	0
	Unpublished	0	0	3††	2††	0	0
Glipizide CDSCO approval 1998	Published	0	1	0	0	0	0
	Unpublished	0	0	0	0	0	0
Glibenclamide CDSCO approval 1995	Published	1	8††	6	7††	0	1
	Unpublished	0	1	1	0	0	0
Gliclazide CDSCO approval 2005	Published	0	0	0	0	0	0
	Unpublished	0	0	0	0	0	0

Online supplementary tables 3 and 4 provide details of the unpublished trials.

*FDC versus concomitant SDFs=FDC versus concomitant treatment with the FDC components given as SDFs.

†FDC versus monotherapy=FDC versus metformin and/or sulfonylurea monotherapy.

‡FDC versus other=FDC versus a different FDC combination or concomitant treatment.

§FDC versus FDC=same FDC components but comparing different dosages or formulations.

¶Other=same FDC but under different trial conditions, for example, fed versus fasting conditions.

**Experimental versus marketed=experimental (new) FDC versus previously marketed FDC.

††Trials (7) with multiple comparator arm categories in the same study.

CDSCO, Central Drugs Standard Control Organization; FDC, fixed-dose combinations; SDF, single-drug formulations.

four criteria which we considered are generally necessary for evaluating the safety and efficacy evidence derived from clinical trials, relating to the size, duration, design and adverse reactions:

- ▶ **Size:** the WHO's International Clinical Trials Registry Platform describes efficacy studies as being conducted in 'large groups' of people 'from several hundred to several thousand'.
- ▶ **Duration:** the WHO guidelines state the minimum trial duration, if the FDC is intended for long-term use, is 6 months.
- ▶ **Design:** the WHO guidelines ask whether the combination has an advantage over the individual components.
- ▶ **Adverse reactions:** the WHO guidelines advocate the benefits should outweigh the potential adverse events.

We determined whether (1) there was a significant difference in the study outcome for the FDC over the comparator treatment, (2) the proportions of participants on the FDC experiencing adverse events or symptoms of hypoglycaemia were reported, (3) the study had balanced the advantages and disadvantages of the FDC over the comparator treatment, and (4) evidence and argument were presented to show that benefits outweighed potential adverse events.^{19 25}

None of the 25 published clinical trials met all four selected WHO FDC criteria (table 3; see online supplementary table 2). Table 3 shows each published trial against the WHO approval criteria for sample size, study duration, study design and that benefits should outweigh potential adverse events. For sample size, only 8 of the 25

trials met our minimum number of subjects criterion of greater than 300 subjects and only 2 had more than 500 subjects. Ten of the 25 trials met the minimum duration criterion of 6 months; only 4 were of 12-month duration. Of these only three met both the minimum number of subjects and minimum duration.²⁶⁻²⁸

Of the 25 trials, only one had been designed to show advantage over individual components. The single trial comparing the metformin/glibenclamide FDC with metformin and glibenclamide used concomitantly as SDFs among 40 patients over 2 weeks found lower 2-hour postprandial glucose levels with the FDC, but the difference was not significant.²¹ Ten trials published data demonstrating each drug contributed to an overall advantage of the FDC over individual components by comparing the FDC with monotherapy. Of the remaining 14 trials, 6 compared the FDC with another FDC, seven compared it with the same FDC at a different dosage or formulation, and one compared the FDC with a previously marketed FDC. To determine whether retrieved trials had presented a suitable argument for balancing the advantages and disadvantages of using an FDC over a standard oral hypoglycaemic treatment, we looked at the change in HbA1c versus the comparator arm, reported adverse events and incidents of hypoglycaemia to determine if an explanation of a balance of advantages and disadvantages was presented, and if a balance of harms and benefits of the experimental treatment was taken into account. Of the 25 trials, 14 reported a significant decrease in HbA1c levels with a metformin FDC versus monotherapy. Thirteen trials reported both frequency of

Table 3 Evaluation of published trials against four selected WHO general principles for approval of FDCs sorted by FDC components

Year of publication; country of study; sponsor	Minimum number of subjects (≥300)*	Minimum duration (≥6 months)†	Designed to show advantage over individual components given concomitantly as SDFs or monotherapy‡	Effects of the FDC§		
				Significant decrease in HbA1c for FDC vs comparator(s) (P value vs comparator)	Percentage of patients reporting adverse events with FDC(s) (P value vs comparator)	Percentage of patients reporting hypoglycaemia with FDC(s) (P value vs comparator)
2001; France; Hoechst Marion Roussel ²⁹	372	5	x (1) Metformin SDF (2) Glimepiride SDF (3) FDC (glimepiride/metformin)	✓ Yes (metformin and glimepiride) (P<0.001)	31% vs 29% (metformin) and 25% (glimepiride) (P value NR)	22% vs 11% (metformin) and 13% (glimepiride) (P=0.039)
2009; Mexico; Laboratorios Silanes ³¹	152	12	x (1) FDC (glimepiride/metformin) (2) FDC (glibenclamide/metformin)	✓ Yes (P=0.025)	69.7% vs 68.4% (glibenclamide) (P=0.851)	17.1% vs 28.9% (glibenclamide) (P=0.047)
2009; India; not listed ^{22,¶}	28	3	x (1) FDC (glimepiride/metformin) (2) FDC (glibenclamide/metformin)	✓ Yes (P value NR)	0% vs 0% (glibenclamide) (P value NR)	17.64% vs 27.27% (glibenclamide) (P value NR)
2011; India; not listed ²³	101	3	x (1) metformin+insulin (2) FDC (glimepiride/pioglitazone/metformin)	x No	0% vs 0% (metformin+insulin) (P value NR)	0% vs 0% (metformin+insulin) (P value NR)
2005; India; Unichem Laboratories ²⁴	101	2	x (1) FDC (glimepiride/pioglitazone/metformin) (2) No comparator	x No	7.9% (P value NR)	NR
2003; USA; Bristol-Myers Squibb ³⁴	246	4.5	x (1) Metformin SDF (2) Glipizide SDF (3) FDC (glipizide/metformin)	✓ Yes (metformin and glipizide) (P<0.001)	63.2% vs 73.3% (metformin) and 67.9% (glipizide) (P value NR)	12.6% vs 1.3% (metformin) and 0% (glipizide) (P value NR)
2002; USA; Bristol-Myers Squibb ³⁵	639	4	x (1) Metformin SDF (2) Glibenclamide SDF (3) FDC (dose 1) (glibenclamide/metformin) (4) FDC (dose 2) (glibenclamide/metformin)	✓ Yes (metformin and gly) (P<0.001)	NR (67% of total participants)	6.8% vs <1% (metformin) and 1.8% (glibenclamide) (P value NR)
2004; USA; Bristol-Myers Squibb ²⁶	310	12	x (1) FDC (dose 1) (glibenclamide/metformin) (2) FDC (dose 2) (glibenclamide/metformin)	x No	NR (79% of total participants)	NR (1 patient total)
2006; USA; Bristol-Myers Squibb ³⁶	50	5	x (1) Metformin SDF (2) Glibenclamide SDF (3) FDC (glibenclamide/metformin)	✓ No	44% vs 87% (metformin) and 65% (glibenclamide) (P value NR)	11% vs 29% (glibenclamide) (P value NR)
2006; Italy; not listed ³⁷	198	6	x (1) FDC (dose 1) (glibenclamide/metformin) (2) FDC (dose 2) (glibenclamide/metformin)	x No	3.6% (P value NR)	11.2% (P value NS)

Continued

Table 3 Continued

Year of publication; country of study; sponsor	Minimum number of subjects (≥300)*	Minimum duration (≥6 months)†	Designed to show advantage over individual components given concomitantly as SDFs or monotherapy‡	Effects of the FDC§		
				Significant decrease in HbA1c for FDC vs comparator(s) (P value vs comparator)	Percentage of patients reporting adverse events with FDC(s) (P value vs comparator)	Percentage of patients reporting hypoglycaemia with FDC(s) (P value vs comparator)
2007; Taiwan; Orient Europharma ³⁸	100	x	<ul style="list-style-type: none"> (1) Metformin SDF (2) Glibenclamide SDF (3) FDC (dose 1) (glibenclamide/metformin) (4) FDC (dose 2) (glibenclamide/metformin) 	Yes (dose 1: P=0.002 vs metformin, P<0.001 vs gly dose 2; P=0.005 vs metformin, P<0.001 vs gly)	NR (98 episodes total)	7.7% vs 8.3% (metformin) (P value NR)
2007 and 2008; Italy; Takeda Italy ^{39,40,¶}	250	x	<ul style="list-style-type: none"> (1) FDC (glibenclamide/metformin) (2) FDC (pioglitazone+metformin or sulfonylurea) 	No	21.3% vs 20.6% (pioglitazone) (P>0.05)	1.3% vs 0% (pioglitazone) (P value NR)
2004; USA; Bristol-Myers Squibb ²⁷	365	✓	<ul style="list-style-type: none"> (1) FDC (glibenclamide/metformin) (2) FDC (glibenclamide/metformin+rosiglitazone) 	No	NR	25% vs 53% (glibenclamide+rosiglitazone) (P value NR)
2004; USA; Bristol-Myers Squibb ^{21,††}	40	x	<ul style="list-style-type: none"> (1) Glibenclamide+metformin (2) FDC (glibenclamide/metformin) 	NR	NR	NR
1999; Italy; Laboratori Guidotti SpA, Pisa ⁴¹	40	✓	<ul style="list-style-type: none"> (1) Glyburide SDF (2) FDC (glibenclamide/metformin) 	Yes (P<0.01)	NR	NR
2003; Mexico; not listed ⁴²	19	x	<ul style="list-style-type: none"> (1) FDC (brand 1) (glibenclamide/metformin) (2) FDC (brand 2) (glibenclamide/metformin) 	NR	NR	NR
2002; USA; Bristol-Myers Squibb ⁴³	806	✓	<ul style="list-style-type: none"> (1) Placebo (2) Metformin SDF (3) Glibenclamide SDF (4) FDC (dose 1) (glibenclamide/metformin) (5) FDC (dose 2) (glibenclamide/metformin) 	Yes (dose 1: P=0.006 vs metformin dose 2: P<0.001 vs metformin P=0.037 vs gly)	NR (69 episodes total)	24.7% vs 21.3% (gly) (P value NR)
2003; USA; Bristol-Myers Squibb ⁴⁴	486	✓	<ul style="list-style-type: none"> (1) Metformin SDF (2) Glibenclamide SDF (3) FDC (glibenclamide/metformin) 	Yes (metformin and gly) (P=0.0003)	78.8% vs 73.2% (metformin) and 75.5% (gly) (P value NR)	57.6% vs 17.7% (metformin) and 39.1% (gly) (P value NR)
2006; USA; Bristol-Myers Squibb ²⁸	318	✓	<ul style="list-style-type: none"> (1) FDC (glibenclamide/metformin) (2) Metformin+rosiglitazone 	Yes (P<0.001)	68% vs 63% (metformin+rosiglitazone) (P value NR)	74% vs 26% (metformin+rosiglitazone) (P value NR)
2009; Mexico; Laboratorios Silanes ^{30,**}	152	x	<ul style="list-style-type: none"> (1) FDC (glibenclamide/metformin) (2) FDC (glimepiride/metformin) 	No	68.4% vs 69.7% (glimepiride) (P=0.851)	28.9% vs 17.1% (glimepiride) (P=0.047)

Continued

Table 3 Continued

Year of publication; country of study; sponsor	Minimum number of subjects (≥300)*	Minimum duration (>6 months)†	Designed to show advantage over individual components given concomitantly as SDFs or monotherapy‡	Effects of the FDC§			
				Significant decrease in HbA1c for FDC vs comparator(s) (P value vs comparator)	Percentage of patients reporting adverse events with FDC(s) (P value vs comparator)	Percentage of patients reporting hypoglycaemia with FDC(s) (P value vs comparator)	
2002; Europe; Merck Lipha ⁴⁵	411	4	x	✓	Yes (metformin and glibenclamide) (P<0.05)	45.1% vs 40% (metformin) and 43% (glibenclamide) (P value NR)	12.3% vs 1% (metformin) and 8% (glibenclamide) (P value NR)
2002; Mexico; not listed ⁴⁶	122	1	x	x	NR	NR	3.3% (P value NR)
1996; Greece; not listed ⁴⁷	30	6	✓	x	Yes (P<0.02)	NR	NR
2009; India; not listed ^{22**}	28	3	x	x	No	0% vs 0% (glimiperide) (P value NR)	27.27% vs 17.65% (glimiperide) (P value NR)
2002; Italy; Laboratori Guidotti SpA, Pisa ⁴⁸	80	12	✓	✓	Yes (metformin and glibenclamide) (P<0.0001)	NR	NR (11.3% of total participants)
Total meeting criteria	8	10	10	10			

**Studies investigate the efficacy of the biomedical or behavioural intervention in large groups of human subjects (from several hundred to several thousand)...²⁵ For these purposes, trials involving at least 300 subjects have been regarded as being within the numbers range.

†If the combination is intended for long-term use, data on safety in patients will normally be required for 6 months or longer' (paragraph 6.6.1.8).¹⁹

‡Clinical studies should be designed to determine whether the combination has an advantage over the component actives given alone in a substantial patient population' (paragraph 6.6.1.4).¹⁹ Comparator(s) in clinical trial are listed.

§If there is an increase in the number or severity of adverse reactions to the FDC as compared with those in response to the individual actives given alone, evidence and argument should be presented showing that the advantages outweigh the disadvantages' (paragraph 6.6.1.16).¹⁹ A trial met this guideline if the trial design compared the FDC with monotherapies of the individual components and demonstrated the FDC had better outcome measurements denoted by a statistically significant decrease in HbA1c, the proportion of patients on the FDC who experienced adverse events or symptoms of hypoglycaemia was significantly better than with the comparator treatment, and an explanation of how the FDC is able to balance the advantages and disadvantages over an alternative treatment is provided in the manuscript. P values from each study, if available, are reported for the FDC versus the comparator treatment. Significant P values are in bold.

¶Two publications were evaluated as one because they reported different findings of the same study.^{46,47}

**These two trials are listed twice, under both glimepiride and glibenclamide, as they compare the two treatments.^{22,32}

††This US study published in 2004 was the only trial that compared an FDC with the component SDFs given concomitantly.²¹

FDCs, fixed-dose combinations; HbA1c, haemoglobin A1c; NR, not reported; SDFs, single-drug formulations.

adverse events and symptoms of hypoglycaemia specifically for the FDC. Five studies reported adverse events or hypoglycaemia in aggregate but did not distinguish between treatment arms. Six studies did not report these outcomes and six studies only reported one of the two outcomes. In five trials more than 50% of participants experienced adverse events with FDCs; these were not statistically significant (or not reported) compared with the alternate treatment regimen(s). Three trials reported increased patient compliance as the explanation of benefit for the FDC over the comparator treatment.^{21 23 26} However only one of these studies compared the FDC with concomitant treatment but did not report other supportive outcomes (ie, HbA1c levels, adverse events, hypoglycaemia).²¹ No studies balanced benefits and harms, that is, adverse reactions and clinical outcomes. Additional information on reported safety and efficacy for published trials is presented in online supplementary table 2. Overall, no trials provided enough evidence of safety and efficacy to justify the use of the FDC over concomitant treatments of the same active ingredients.

LACK OF CLINICAL TRIAL EVIDENCE FOR METFORMIN FDCS IN INDIA

None of the published trials included in this review met all four WHO-based criteria (table 3). Despite rigorous searching, we found only one study evaluating the efficacy and safety of a metformin FDC versus concomitant use of the component drugs as SDFs; it was underpowered and of poor quality.²² Most studies only compared metformin FDCs with monotherapies. Overall, more than half of the published trials were conducted in the USA, while only three were conducted in India. Only two trials were published prior to CDSCO approval (glimepiride and glimepiride/pioglitazone), of which only one study was conducted on Indian patients prior to its launch in India.^{24 29} The Indian study evaluated the efficacy of the FDC in just 101 patients with type 2 diabetes over 2 months of treatment.²⁴

The overall lack of publicly available India-specific data heightens the need for publication of unpublished trials with Indian patients (see online supplementary table 2). India has only required registration with CTRI, the national clinical trials database, since 2009. Although unpublished trials are listed in the clinical trial registries, they only provide basic trial information with no results or outcomes reported (see online supplementary table 3). Both national and international databases of clinical trials should be updated routinely. The lack of trials on Indian patients, in particular, is of concern considering CDSCO's guidelines for FDC approvals acknowledge the importance of conducting trials on the Indian population to determine safety and efficacy.

The use of FDCs for treatment of diabetes has been described as an Indian innovation.³⁰ Indeed, sales data show that hundreds of brands of metformin FDCs are on the market in India and outstrip sales of metformin

SDFs in terms of both volume and value.^{4 20} India, therefore, should be at the forefront of regulatory practices. Although stringent pharmaceutical regulatory systems should be in place to protect patients from potentially dangerous medicines, as well as ensure the medicines are effective for the condition being treated, the recent overturning of the government ban on irrational FDCs raises serious questions about the strength of the rules on clinical trials evidence. According to the WHO, FDCs that contain (1) the same active ingredients, (2) in the same doses, (3) as an established regimen of single drugs, (4) with the same dosage regimen, (5) a well-characterised efficacy and safety profile and (6) where the products used in obtaining clinical relevant outcomes have been shown to be of good quality need not 'usually' be trialled. However, given that none of the evaluated published trials provide such evidence, CDSCO should demonstrate how it considers efficacy and safety to have been established. Although it is possible that CDSCO holds reliable evidence supporting metformin FDC approvals and knows the results of the unpublished trials, as is common with regulatory agencies, it should make the evidence and the trial results publicly available.

Our examination of published and unpublished studies of metformin FDCs for type 2 diabetes raises serious questions about the basis of CDSCO approvals as it shows the lack of trial evidence to support the efficacy and safety of the top-selling metformin FDCs approved for marketing, manufacture and sale in India. FDC treatments for diabetes are not recommended by national or international treatment guidelines, yet many metformin FDCs have been approved by CDSCO. In addition, dozens of manufacturers have been licensed by individual States, but as public details of licences are not published we could not explore this further. The finding that three of the five top-selling metformin FDC formulations were launched on the market before CDSCO approval highlights weaknesses in the regulatory processes of both the federal system and the State regulators.

Furthermore, four out of five of these top-selling FDCs were found to be on the list of banned FDCs by the Ministry of Health and Family Welfare from March 2016 (see online supplementary table 1).² Hundreds of manufacturers, including many MNCs, petitioned State courts for a stay on the ban. In December 2016 they succeeded. The Delhi High Court ruled that CDSCO had not followed the appropriate procedures laid out in the Drugs and Cosmetics Act to impose the ban and reversed it, giving companies the ability to reintroduce potentially harmful medicines into the market-place.³¹ This ruling is currently headed to the Supreme Court.

MNCs have played a significant role in the clinical trials of metformin FDCs. Eighteen of the 25 published clinical trials conducted in patients with type 2 diabetes disclosed sponsor funding or were conducted by pharmaceutical companies. Eight different companies were represented as sponsors in the trials, with nine studies sponsored by MNCs. The poor quality of available published trials and

their funding sources raise concerns about the motivation for conducting these trials and whether the sponsors are using them for seeding or marketing purposes to gain a foothold in country markets.³²

CONCLUSION

To our knowledge, this is the first study analysing the availability of published clinical trials evidence on the efficacy and safety of metformin FDCs. Our examination exposes serious deficiencies in the evidence base for metformin FDCs for type 2 diabetes and raises questions about the role of MNCs in manufacturing these for sale and use. To justify metformin FDC approvals and provide confidence in their efficacy and safety, CDSCO should make public the evidence it used in approving the metformin FDCs examined in this review. If that evidence does not extend beyond the trials reviewed here, those FDCs should be banned immediately. If that evidence includes the results of trials not reviewed in this paper, which do not meet the four WHO standards used for evaluation, those FDCs should be banned. Mitigation of any public health consequences of removing widely used diabetes treatments from the market will require collaboration between the regulators, providers as well as drug manufacturers, to ensure that the medicines in the market-place have proven efficacy and safety. It is also necessary for clinical trial databases to be constantly updated with both protocol and outcomes in order to improve transparency of trial data, and for the evidence underpinning drug approvals to be published. Legislation setting out clinical trial requirements for new drugs should be revised to prevent irrational FDCs from entering the market. The government's March 2016 ban on FDCs should be reinstated and a statutorily required review of FDCs established, similar to the one mandated by the US Congress in 1962.

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