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

Valerie Evans,1,2 Peter Roderick,3 Allyson M Pollock3

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(PharmaTrac) were combined with searches through published literature, clinical trial registries, and published and unpublished trial websites of metformin FDCs in adults with type 2 diabetes mellitus.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 Evaluation of published and unpublished clinical trials of these five FDCs found none provided robust evidence of safety and efficacy for the treatment of type 2 diabetes.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 approval system to control the entry and 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 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

Over 60 million people have been diagnosed with type 2 diabetes mellitus in India, which has been described as ‘the diabetes...

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). 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). The ban was lifted in December 2016 by the Delhi High Court and was upheld by the Supreme Court in December 2017. The Supreme Court required the Drugs Technical Advisory Board to consider the banned drugs (except those approved before 1988) and to submit a report within 6 months.

One of the primary arguments for prescribing FDCs for treatment of type 2 diabetes is improved adherence to treatment due to convenience. 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. 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). CDSCO must give permission before manufacture and 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 medicines meet WHO standards is expressed in the Indian government’s rules and should be published immediately in the event of any fDCs without ethical justification. If the evidence does not extend beyond the trials reviewed in this paper, those FDCs should be banned. If that evidence includes the results of trials not reviewed in this paper, those FDCs should be banned.

**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, 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.
- An urgent review of FDCs should be mandated by the Indian Parliament.

**Key questions**

- 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, 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.
- An urgent review of FDCs should be mandated by the Indian Parliament.

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**Figure 1** Timeline of important events concerning the five top-selling metformin fixed-dose combinations in India. CDSCO, Central Drugs Standard Control Organization; US FDA, US Food and Drug Administration.
drugs, including FDCs, are safe and effective was only imposed in 2001.16

**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 2005.15

**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).15 These requirements and categories have been analysed previously, highlighting poor drafting and the downgrading of the rules in 2005.16

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.17 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

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**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 centres.19

<table>
<thead>
<tr>
<th>Trial phase</th>
<th>1988 Schedule Y</th>
<th>2005 Schedule Y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II</td>
<td>‘Normally 10–12 patients should be studied at each dose level. These studies are usually limited to 3–4 centres…’</td>
<td>‘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 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’.</td>
</tr>
<tr>
<td>Phase III</td>
<td>‘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’.</td>
<td>‘(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’.</td>
</tr>
<tr>
<td>Phase IV*</td>
<td>‘In addition, data on adverse drug reactions observed during clinical use of the drug should be collected in 1000–2000 patients…’</td>
<td>‘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’.</td>
</tr>
</tbody>
</table>

*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.
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 ‘Guid-
ance 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’. The document
focuses on the forms and payments that drug companies
must use and make and contain little substantive guid-
ance beyond reiterating the rules, and do not use the
same FDC categories as those set out in Appendix VI of
Schedule Y. Its website also contains a docu-
ment 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.

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 guide-
lines for this type of product’ (see online supplementary
figure 1). While India has had FDC-specific rules since
1988, as well as draft industry guidance and a prelimi-
nary 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. The
following were the resulting five top-selling metformin
FDCs: (1) glibenclamide/metformin, (2) glimepiride/
glitazone/metformin, (3) glibizide/metformin,
(4) glibenclamide/metformin, and (5) glitazide/
metformin. Although all five of these top-selling formul-
ations 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). 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 supple-
mentary figures 2 and 3). After application of inclusion/
 exclusion criteria, 25 publications remained eligible for
inclusion: 3 of glibenclamide/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 unpub-
lished 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 combi-
nation 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/formu-
lation but under fed versus fasting conditions or no
comparator); and (6) new FDC formulation versus previ-
ously marketed FDC (table 2). Only one trial compared
an FDC (glibenclamide/metformin) versus concomitant
treatment with glibenclamide and metformin. 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 glime-
piride/pioglitazone/metformin with metformin plus
insulin or no treatment

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 Combi-
nation Medicinal Products, which was intended to provide
guidance to drug regulatory agencies on robust registra-
tion requirements for FDCs given their growing use in
treating diseases such as HIV, malaria and tuberculosis
(see online supplementary figure 1). On the basis that
diabetes is highly prevalent in India and affects millions
of people, treatment is long term, and risks of hypogly-
caemia and poor tolerance are well-reported, we adopted
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.

Of these only three met both the minimum number of subjects and minimum duration.

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. 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. Thirty trials reported both frequency of adverse events and symptoms of hypoglycaemia in aggregate but did not distinguish between treatment arms. Six studies did not report these...
<table>
<thead>
<tr>
<th>Year of publication; country of study; sponsor</th>
<th>Minimum number of subjects (≥300)*</th>
<th>Minimum duration (≥6 months)†</th>
<th>Designed to show advantage over individual components given concomitantly as SDFs or monotherapy‡</th>
<th>Effects of the FDC§</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001; France; Hoechst Marion Roussel</td>
<td>372</td>
<td>✔</td>
<td>(1) Metformin SDF (2) Glimepiride SDF (3) FDC (glimepiride/metformin) x</td>
<td>Yes (metformin and glimepiride) (P&lt;0.001) 31% vs 29% (metformin) and 25% (glimepiride) (P value NR) 22% vs 11% (metformin) and 13% (glimepiride) (P=0.039)</td>
</tr>
<tr>
<td>2002; USA; Bristol-Myers Squibb</td>
<td>639</td>
<td>✔</td>
<td>(1) Metformin SDF (2) Gliclazide SDF (3) FDC (gliclazide/metformin) x</td>
<td>Yes (metformin and gliclazide) (P&lt;0.001)</td>
</tr>
<tr>
<td>2003; Italy; not listed</td>
<td>198</td>
<td>✔</td>
<td>(1) FDC (dose 1) (glibenclamide/metformin) (2) FDC (dose 2) (glibenclamide/metformin) x</td>
<td>No 6.8% vs &lt;1% (metformin) and 1.8% (glibenclamide) (P value NR)</td>
</tr>
<tr>
<td>2004; USA; Bristol-Myers Squibb</td>
<td>310</td>
<td>✔</td>
<td>(1) FDC (dose 1) (glibenclamide/metformin) (2) FDC (dose 2) (glibenclamide/metformin) x</td>
<td>No (79% of total participants)</td>
</tr>
<tr>
<td>2006; USA; Bristol-Myers Squibb</td>
<td>50</td>
<td>x</td>
<td>(1) Metformin SDF (2) Glibenclamide SDF (3) FDC (glibenclamide/metformin) x</td>
<td>No 44% vs 87% (metformin) and 65% (glibenclamide) (P value NR) 11% vs 29% (glibenclamide) (P value NR)</td>
</tr>
<tr>
<td>2006; Italy; not listed</td>
<td>198</td>
<td>x</td>
<td>(1) FDC (dose 1) (glibenclamide/metformin) (2) FDC (dose 2) (glibenclamide/metformin) x</td>
<td>No 3.6% (P value NR) 11.2% (P value NS)</td>
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Continued
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<tr>
<th>Year of publication; country of study; sponsor</th>
<th>Minimum number of subjects (≥300)*</th>
<th>Minimum duration (≥6 months)†</th>
<th>Designed to show advantage over individual components given concomitantly as SDFs or monotherapy‡</th>
<th>Effects of the FDC§</th>
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<tr>
<td>2007; Taiwan; Orient Europharma</td>
<td>100</td>
<td>x</td>
<td>(1) Metformin SDF (2) Glibenclamide SDF (3) FDC (dose 1) (glibenclamide/metformin) (4) FDC (dose 2) (glibenclamide/metformin)</td>
<td>✔</td>
</tr>
<tr>
<td>2007 and 2008; Italy; Takeda Italy</td>
<td>250</td>
<td>x</td>
<td>(1) FDC (glibenclamide/metformin) (2) FDC (pioglitazone+metformin or sulfony lurea)</td>
<td>✔</td>
</tr>
<tr>
<td>2004; USA; Bristol-Myers Squibb</td>
<td>365</td>
<td>✔</td>
<td>(1) FDC (glibenclamide/metformin) (2) FDC (glibenclamide/metformin+rosiglitazone)</td>
<td>✔</td>
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<tr>
<td>1999; Italy; Laboratori Guidotti SpA, Pisa</td>
<td>40</td>
<td>x</td>
<td>(1) Glyburide SDF (2) FDC (glibenclamide/metformin)</td>
<td>✔</td>
</tr>
<tr>
<td>2003; Mexico; not listed</td>
<td>19</td>
<td>x</td>
<td>(1) FDC (brand 1) (glibenclamide/metformin) (2) FDC (brand 2) (glibenclamide/metformin)</td>
<td>✔</td>
</tr>
<tr>
<td>2002; USA; Bristol-Myers Squibb</td>
<td>806</td>
<td>✔</td>
<td>(1) Placebo (2) Metformin SDF (3) Glibenclamide SDF (4) FDC (dose 1) (glibenclamide/metformin) (5) FDC (dose 2) (glibenclamide/metformin)</td>
<td>✔</td>
</tr>
<tr>
<td>2003; USA; Bristol-Myers Squibb</td>
<td>486</td>
<td>✔</td>
<td>(1) Metformin SDF (2) Glibenclamide SDF (3) FDC (glibenclamide/metformin)</td>
<td>✔</td>
</tr>
<tr>
<td>2006; USA; Bristol-Myers Squibb</td>
<td>318</td>
<td>✔</td>
<td>(1) FDC (glibenclamide/metformin) (2) Metformin+rosiglitazone</td>
<td>✔</td>
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</table>
Table 3 Continued

<table>
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<tr>
<th>Year of publication; country of study; sponsor</th>
<th>Minimum number of subjects (≥300)*</th>
<th>Minimum duration (≥6months)†</th>
<th>Designed to show advantage over individual components given concomitantly as SDFs or monotherapy‡</th>
<th>Effects of the FDC§</th>
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</thead>
<tbody>
<tr>
<td>2009; Mexico; Laboratorios Silanes†**</td>
<td>152</td>
<td>x</td>
<td>✔</td>
<td>No</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(1) FDC (glibenclamide/metformin)</td>
<td>Significant decrease in HbA1c for FDC vs comparator(s) (P value vs comparator)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(2) FDC (glimepiride/metformin)</td>
<td>68.4% vs 69.7% (glimepiride) (P=0.851)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>✔</td>
<td>28.9% vs 17.1% (glimepiride) (P=0.047)</td>
</tr>
<tr>
<td>2002; Europe; Merck &amp; Co*</td>
<td>411</td>
<td>✔</td>
<td>✔</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1) Metformin SDF</td>
<td>Percentage of patients reporting adverse events with FDC(s) (P value vs comparator)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) Glibenclamide SDF</td>
<td>45.1% vs 40% (metformin) and 43% (glibenclamide) (P value NR)</td>
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<td></td>
<td></td>
<td></td>
<td>(3) FDC (dose 1) (1) glibenclamide/metformin</td>
<td>12.3% vs 1% (metformin) and 8% (glibenclamide) (P value NR)</td>
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<td></td>
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<td>(4) FDC (dose 2) (1) glibenclamide/metformin</td>
<td></td>
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<tr>
<td>2002; Mexico; not listed††</td>
<td>122</td>
<td>x</td>
<td>✔</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1) FDC (dose 1) (1) glibenclamide/metformin</td>
<td>Percentage of patients reporting hypoglycaemia with FDC(s) (P value vs comparator)</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>(2) FDC (dose 2) (1) glibenclamide/metformin</td>
<td>3.3% (P value NR)</td>
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<td>(3) FDC (dose 3) (1) glibenclamide/metformin</td>
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<tr>
<td>1996; Greece; not listed‡‡</td>
<td>30</td>
<td>x</td>
<td>✔</td>
<td>Yes</td>
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<tr>
<td></td>
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<td></td>
<td>(1) FDC (glibenclamide/metformin)</td>
<td>Percentage of patients reporting adverse events with FDC(s) (P value vs comparator)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) FDC (phenformin/metformin)</td>
<td>(P&lt;0.02)</td>
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<td></td>
<td>✔</td>
<td>NR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(1) FDC (glibenclamide/metformin)</td>
<td>Percentage of patients reporting hypoglycaemia with FDC(s) (P value vs comparator)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(2) FDC (glimepiride/metformin)</td>
<td>NR</td>
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<tr>
<td></td>
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<td></td>
<td>✔</td>
<td>NR</td>
</tr>
<tr>
<td>2009; India; not listed††‡‡</td>
<td>28</td>
<td>x</td>
<td>✔</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1) FDC (glibenclamide/metformin)</td>
<td>Percentage of patients reporting adverse events with FDC(s) (P value vs comparator)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) FDC (glimepiride/metformin)</td>
<td>(P&lt;0.0001)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>✔</td>
<td>0% vs 0% (glimepiride) (P value NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1) Metformin SDF</td>
<td>27.27% vs 17.65% (glimepiride) (P value NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) Glibenclamide SDF</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(3) FDC (glibenclamide/metformin)</td>
<td></td>
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<tr>
<td>2002; Italy; Laboratori Guidotti SpA, Pisa*</td>
<td>80</td>
<td>x</td>
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<tr>
<td></td>
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<td></td>
<td>(1) Metformin SDF</td>
<td>Percentage of patients reporting hypoglycaemia with FDC(s) (P value vs comparator)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) Glibenclamide SDF</td>
<td>(metformin and glibenclamide) (P value NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(3) FDC (glibenclamide/metformin)</td>
<td></td>
</tr>
<tr>
<td>Total meeting criteria</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
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</table>

* ‘Studies investigate the efficacy of the biomedical or behavioural intervention in large groups of human subjects (from several hundred to several thousand)…’ 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).
‡ ‘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).
§ ‘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). 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.
** These two trials are listed twice, under both glimepiride and glibenclamide, as they compare the two treatments.
†† This US study published in 2004 was the only trial that compared an FDC with the component SDFs given concomitantly.
FDCs, fixed-dose combinations; HbA1c, haemoglobin A1c; NR, not reported; SDFs, single-drug formulations.
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. 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. The Indian study evaluated the efficacy of the FDC in just 101 patients with type 2 diabetes over 2 months of treatment.

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 Clinical Trials Registry - India, 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. 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. 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). Hundreds of manufacturers, including many MNCs, petitioned State courts for a stay on the ban. In December 2016 they succeeded. The Delhi High Court lifted the ban giving companies the ability to reintroduce potentially harmful medicines into the market-place. This ruling was upheld by the Supreme Court in December 2017 when remitting the matter for the consideration of the Drugs Technical Advisory Board.

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...
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-reviewed request of FDCs established, similar to the one mandated by the US Congress in 1962.

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Contributors AMP conceived the study. PR contributed to the portion of the manuscript regarding regulation. VC conducted the literature search and data extraction, and drafted the manuscript. All authors contributed to the analysis, review, and drafting of the manuscript and approval of the final submission.

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Data sharing statement Clinical trial data presented in this paper are publicly available through publications or clinical trial databases. PharmaTrac data can be obtained by contacting AIICO Pharmassofttech AWACS Pvt. Ltd. directly.

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