

## India should introduce a new Drugs Act

The 2013 Indian Drugs and Cosmetics (Amendment) Bill will not deliver rational, safe, and effective regulation of drugs, according to a new analysis by legal and health experts.



Policy makers in India are grappling with how best to address the serious problems facing the country's drug regulation system. Reports have repeatedly highlighted multiple concerns, including weak regulatory infrastructure and poor performance, lack of access to safe and effective medicines, badly regulated clinical trials, and the proliferation of fixed-dose combinations (FDCs)—formulations comprised of two or more drugs combined in a fixed ratio of doses and available in a single-dosage form.

The Drugs and Cosmetics (Amendment) Bill introduced in the Indian Parliament in August, 2013, is the latest attempt to deal with some of the concerns. Last month, two of its key proposals—creation of a new Central Drugs Authority with greater powers than the current regulator, the Central Drugs Standard Control Organisation (CDSCO), and extension of the regulatory system to cover exported medicines—were rejected by the same parliamentary committee whose scathing criticism of CDSCO in May, 2012, ushered in the Bill.

In 2012, India's Standing Committee on Health and Family Welfare criticised CDSCO's mission to "meet the aspirations...demands and requirements of the pharmaceutical industry" and its apparently close cooperation with applicants in easing drug approvals and avoiding legal requirements. The Committee was also critical of marketing approvals being granted without clinical trials (especially trials in Indian populations), and was concerned about the "very large number" of FDCs that had been approved by State regulators without prior CDSCO approval. FDCs are a remarkable feature of the Indian pharmaceutical market, with rising approvals reported between 1999 and 2011.

We analysed drug approvals over 42 years in India and examined the development of the country's drug laws over seven decades to assess whether legal changes could explain trends in approvals. We evaluate the 2013 Bill in view of the findings.

**"The regulatory environment with its many deficiencies is likely to have facilitated the peak in approvals..."**

### New drug approvals 1971–2012

From 1971–2012, 2972 approvals were granted by CDSCO, 63% (1874) for single-dose formulations (SDFs) and 37% (1098) for FDCs. Annual approvals were highest for both SDFs and FDCs during a 7 year period from 2005–11 (figure); 41% (763 of 1874) of SDF approvals and 63% (689 of 1098) of FDC approvals were granted during this time. Approvals in 2012 were considerably lower for both SDFs (35) and FDCs (9).

India re-introduced product patents for drugs in 2005. It seems unlikely, however, that this development could have contributed to the 2005–11 spike in approvals or to the comparatively high percentage of FDCs approved. The regulatory environment with its many

deficiencies is likely to have facilitated the peak in approvals, as the following conclusions from our assessment of the country's laws show.

### India's drug laws

When examining India's drug laws, several conclusions stand out. First, the current Drugs and Cosmetics Act is old and deficient. The core primary legislation presently regulating drugs was passed in 1940 and has been amended at least ten times. It contains no duty on the regulator to be satisfied about the safety and effectiveness of a drug before marketing. This duty was only introduced for new drugs in secondary rules in 2001. Additionally, the 2013 Bill continues the current Act's confusion between the concepts of effectiveness and efficacy, by proposing the latter in a new long title to the Act. The Cochrane Collaboration defines efficacy as the "extent to which an intervention produces a beneficial result under ideal conditions", and effectiveness as the "extent to which a specific intervention, when used under ordinary circumstances, does what it is intended to do". In requiring new drugs to be "effective for use" since 2001, India's rules have imposed a high standard that should not be confused with "efficacy" which applies in ideal

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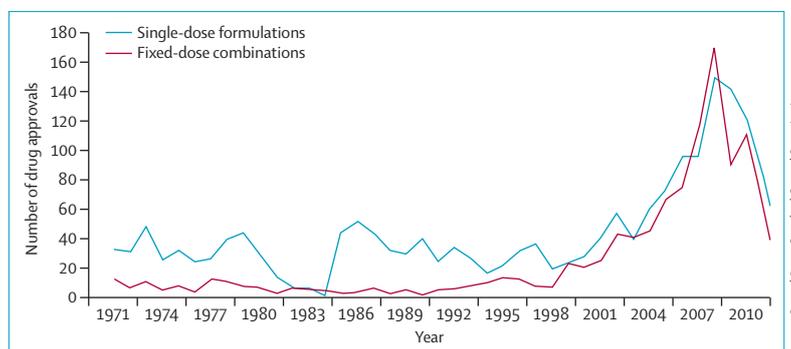


Figure: New drug approvals granted in India from 1971–2012 (single-dose formulations and fixed-dose combinations)

**Panel 1: Types of fixed-dose combinations (FDCs) and their data submission requirements for approval according to the 1988 Rules**

Appendix VI to Schedule Y of the Drugs and Cosmetics Rules 1945, as inserted by the Drugs and Cosmetics (Eight (sic) Amendment) Rules 1988, identifies four types of FDC.

**Type 1**

The first group of FDC includes those in which one or more of the active ingredients is a new drug. Such FDCs are treated in the same way as any other new drug, both for clinical trials and for making permission.

**Type 2**

The second group of FDC includes those in which active ingredients already approved or marketed individually are combined for the first time, for a particular claim and where the ingredients are likely to have significant interaction of a pharmacodynamic or pharmacokinetic nature. For permission to undertake clinical trials with such FDC, a summary of available pharmacological, toxicological, and clinical data on the individual ingredients should be submitted, along with the rationale for combining them in the proposed ratio. In addition, acute toxicity data (LD 50) and pharmacological data should be submitted on the individual ingredients as well as their combination in the proposed ratio. If clinical trials have been done with the FDC in other countries, reports of such trials should be submitted. If the FDC is marketed abroad, the regulatory status in other countries should be stated. For marketing permission, the reports of clinical trials done with the FDC in India should be submitted. The nature of trials depend on the claims to be made and the data already available.

**Type 3**

The third group of FDC includes those which are already marketed, but in which it is proposed either to change the ratio of active ingredients or to make a new therapeutic claim. For such FDCs, the appropriate rationale should be submitted to obtain a permission for clinical trials, and the reports of trials should be submitted to obtain a marketing permission. The nature of trials depends on the claims to be made and the data already available.

**Type 4**

The fourth group of FDC includes those whose individual active ingredients have been widely used in a particular indication for years, their concomitant use is often necessary and no claim is proposed to be made other than convenience, and a stable acceptable dosage form and the ingredients are unlikely to have significant interaction of a pharmacodynamic or pharmacokinetic nature. No additional animal or human data are generally required for these FDCs, and marketing permission may be granted if the FDC has an acceptable rationale.

clinical conditions and is generally determined in trials done in tightly defined populations. The 2013 Bill, however, does just that, undermining the need for evaluation of effectiveness.

Second, problems exist with increasing central control of drug regulation. Slowly but surely over time, the initial clarity of responsibility between central government (responsible for imported drugs) and the States (responsible for manufacture, distribution, and sale) has become blurred as central control increased. In 1952, rules introduced the concept of a new drug, requiring applicants to have the written permission of the central regulator before import. In 1960, the central government assumed the power to

issue directions to States. In June, 1961, the rules were further amended to prohibit manufacture of a new drug without the approval of the central regulator who was given discretion to require submission of supporting clinical trial data. Amendments to the Act in 1982 and 2008 gave the central government power to regulate, restrict, or prohibit drugs on specified grounds in the public interest.

The 2013 Bill would increase central control further, and this has been interpreted as giving more influence and power to multinational companies (MNCs). It has been opposed by Shri Jagdeep Singh, president of the SME (small-medium enterprises) Pharma Industries Confederation: "the centralisation of drug licensing would

kill the SME pharma units and further strengthen the already powerful MNCs. There was no level-playing field and the big pharma players were making the survival of SME pharma companies difficult."

Third, India has badly drafted and weak rules on clinical trials, which were weakened further in 2005. Since the 1988 amendment Rules, the general legal position has been that clinical trials must be done for all "new drug substances" from phase 1 onwards if they are "discovered" in India; phase 3 trials are necessary if they are "discovered in other countries". However, the rules are badly drafted— anecdotally, with pharmaceutical industry input—and the language used is often non-mandatory, descriptive not prescriptive, and in the passive voice. In 2005, references to minimum numbers or ranges for trial participants and sites were removed. The new Bill overlooks these flaws, focusing only on how clinical trials are undertaken rather than also on when they are needed.

Furthermore, India's current Drug Act allows the central regulator to exercise discretions that are not subject to transparency and accountability mechanisms. In 1988, the rules gave the central regulator, CDSCO, power to override "the requirement of submitting the result of local clinical trials...if the drug is of such a nature that the licensing authority may, in public interest decide to grant such permission on the basis of data available from other countries" (the public interest override). In 2005, CDSCO was given another, potentially overlapping, discretion to override the data submission rules, focusing on the seriousness and relevance to India of the diseases that the new drugs treated (the disease override). CDSCO is not obliged to explain or make public its reasoning when deciding to exercise these discretions. The 2013 Bill does nothing to address these issues, which have been severely criticised, particularly with regards to the lack of trials in Indian populations.

## The particular problem of FDCs

Official concern about FDCs dates back more than 30 years. The 1940 Act, as amended, does not mention FDCs and provisions regulating them were first introduced into rules in 1988. These provisions are particularly badly drafted and have been amended several times since. In 2001, the safety and effectiveness duty on the regulator was imposed; in 2005, data submission requirements were downgraded. Our analysis has exposed problems in three areas.

First, the scope of FDCs covered in the 1988 Rules is contradictory and unclear. Since 1988, applications for permission to import or manufacture FDCs of “drugs already approved as individual drugs” are made to CDSCO, with data submission requirements set out in Appendix VI of Schedule Y of the Drugs and Cosmetics Rules 1945. However, remarkably, none of the four types of FDCs included in Appendix VI require the active ingredients to have been individually approved previously (panel 1). Moreover, only two types of FDC were included within the definition of a new drug; and they are not described in the same language as the four types in Appendix VI. Of these, type 4 FDCs, where “no claim is proposed to be made other than convenience” are of the greatest concern owing both to the absence of a requirement for supporting safety or effectiveness data and to widening of the grouping in 2005 to include FDCs in which the individual active ingredients “or drugs from the same class” have been widely used in a particular indication(s) for years. The 2013 Bill does nothing to remove the contradictions in FDC types or to address the huge effectiveness and safety deficiencies permitted in the type 4 “convenience” classification.

Second, data submission requirements for approvals were downgraded in 2005 (appendix). The four FDC types in Appendix VI have different data submission provisions. As well as extending the scope of

the type 4 convenience FDCs, the 2005 amendments downgraded requirements for type 1 FDCs, stating that they should be treated in a “similar” way to any new drug rather than in the “same” way, losing the clarity of the 1988 version and replacing it with an ambiguous term, while erroneously, but perhaps tellingly, describing these requirements as “marketing data”.

The 2005 amendments also omitted the reference to trials in Indian patients for type 2 FDCs and omitted any reference to any trials for type 3 FDCs, signalling less emphasis on the need to undertake these studies. This downgrade is of particular concern in the case of type 2 FDCs, as this category purports to apply to FDCs where substantial pharmacodynamic or pharmacokinetic interactions are considered likely. The 2013 Bill does not address any of these issues.

Finally, India’s regulation of FDCs is inconsistent with WHO guidelines for registration of fixed-dose combination medicinal products. WHO guidelines on FDCs post-date the 2005 amendments to the Indian Act. Classification of FDC types is approached differently by WHO (panel 2), with four scenarios, based on whether the safety and efficacy of the active ingredients has already been established. In contrast, Indian FDC types 2 and 4, for example, turn on substantive factors, namely the likelihood of substantial pharmacodynamic or pharmacokinetic interactions, and convenience. Broadly, Indian FDC type 1 corresponds with WHO scenario 4; types 2 and 3 seem to correspond loosely with scenario 3, but the Indian types use previous approval or marketing (type 2) and marketing (type 3) instead of established safety and effectiveness or even efficacy; type 4, (convenience FDCs) has no WHO classification equivalent.

The WHO guidelines suggest an approach in which FDC advantages and disadvantages are identified and

### Panel 2: FDC groupings according to WHO guidelines

An application to register a fixed-dose combination finished pharmaceutical product (FDC-FPP) may fall into any one of the following four scenarios. There are different requirements for each scenario.

*Scenario 1.* The new FDC-FPP contains the same actives in the same doses as an existing FDC-FPP; that is it is a “generic” of the existing FDC-FPP; they are “multisource” products. The quality, safety and efficacy of the existing product have been established.

*Scenario 2.* The new FDC-FPP contains the same actives in the same doses as an established regime of single entity products, and the dosage regimen is the same. Alternatively, the established regime may involve combinations of single entities and FDCs, for example, a single entity FPP combined with an FDC-FPP that contains two actives. In all cases, the established regime has a well-characterised safety and efficacy profile, and all of the FPPs used in obtaining clinical evidence have been shown to be of good quality.

*Scenario 3.* The new FDC-FPP combines actives that are of established safety and efficacy but have not previously been used in combination for this indication. The new FDC-FPP comprises a combination for which safety and efficacy have been established, but that will be used in a different dosage regimen.

*Scenario 4.* The new FDC-FPP contains one or more new chemical entities.

WHO Technical Report Series, No. 929, 2005. WHO Expert Committee on Specifications for Pharmaceutical Preparations, 39th Report.

the evidence for each considered and weighed and included in the submission for approval.

The guidelines also distinguish between positive scientific and medical factors, and cost and procurement factors advising that the latter “alone are not sufficient reason to approve a FDC if it has not been justified by appropriate data and on scientific and medical principles”. The Indian rules do not adopt a similar approach. Moreover, elevating an FDCs “convenience” as a basis for approval is inconsistent with WHO guidelines which list convenience as only one of many specified factors to be weighed.

WHO guidelines suggest that safety and efficacy data should be submitted for FDCs in scenarios 3 and 4 and “not usually” for FDCs in scenarios 1 and 2 but advise that each application should be considered by regulators on its merits using scientific judgment

See Online for appendix

### Panel 3: Recommendations for amendments to the Indian Drugs and Cosmetics (Amendment) Bill 2013

- Give the new Central Drugs Authority a statutory purpose, which would include approving safe, effective, and high-quality drugs that are medically needed and therapeutically justified
- Impose a duty on the regulator to be satisfied that new drugs including fixed-dose combinations (FDCs) are safe, effective, of requisite high quality and medically needed before they are approved
- Set out a framework within which the regulator would be required to prioritise consideration of applications for new drug approvals based on national need and therapeutic justification
- Make clear when clinical trials are necessary, especially for FDCs and especially in Indian patients
- Re-frame the scope of the public interest and disease overrides, and impose accountability mechanisms on the regulator, such as a duty to provide written and published reasons when the discretions are exercised
- Make new drug approvals initially provisional for a specified and limited period of time, followed by a confirmed approval if effectiveness is shown in evidence gained during the period arising from real-world use of the drug
- Align India's FDC laws more closely with WHO guidelines, in particular by reclassifying FDCs based on established safety and effectiveness grounds, and by requiring the balancing of advantages and disadvantages
- Require a review of the safety and effectiveness of all currently available FDCs, not unlike the legally required review mandated by the US Congress in 1962
- Require a periodic review of drugs on the Indian market to assess their continued relevance to the medical needs of the population

and logical argument. In India, the 2005 amendments to Appendix VI stand in stark contrast, seemingly sidestepping any requirements to undertake clinical trials.

#### A new Drugs Act

Imprecise 1988 provisions and lax 2005 amendments might have laid the regulatory ground for record numbers of SDF and FDC approvals in India between 2005 and 2011. Of particular concern, 2005 saw a weakening of clinical trial provisions, introduction of a second discretion for CDSCO (not linked to any transparency mechanism) to override data submission requirements, weakening of FDC data requirements, and widening of the convenience FDC type. CDSCO does not disclose the evidence base for applications it approves or rejects. Neither does it publish a list of FDC approvals by type. It was not therefore possible to analyse which clinical trial provisions

had been applied to which approval decisions, which data submission provisions had been applied to which FDC applications, how the data had been interpreted, or whether the public interest or disease overrides had been applied. In the interests of public confidence, CDSCO must publish the safety and effectiveness evidence it used to justify approval of SDFs and FDCs, and its reasons for exercising discretionary overrides where it has done so.

The 2013 amendment Bill is silent on these issues, as it is on all of the regulatory problems highlighted in this report. It is also striking that last month's report on the Bill by India's Standing Committee on Health and Family Welfare did not raise any of these issues or problems.

The 2013 Bill is of particular concern because it does not propose to give the new Central Drugs Authority a statutory purpose or objective, neither does it require the regulator

to be satisfied of the effectiveness of new drugs, and compounds the current Act's failure to take seriously the distinction between the effectiveness and efficacy of drugs. Randomised controlled trials which are typically used as the basis for marketing approval generally show efficacy rather than effectiveness. As a logical consequence, marketing approvals should, in the first instance, be provisional and for a specified and limited period of time, and should lapse after expiry of that period. A confirmed approval should be given if effectiveness is shown using evidence gained during real-world use of the drug. This measure would respect the important difference between efficacy and effectiveness, would provide a substantial incentive for effective post-marketing surveillance, and would be an important global advance in drug regulation.

The Drugs and Cosmetics (Amendment) Bill 2013 fails to provide a rigorous foundation for putting effectiveness, safety, rationality, and need at the heart of India's drug regulatory system. Indeed, it does not even attempt it. Rather, it is another patch on the 74-year-old, pre-Independence Act whose structural design has arguably been stretched beyond breaking point.

Lawmakers might wish to consider further amendments to the Bill to strengthen its provisions from a public health perspective, and so we set out some recommendations (panel 3).

However, truly effective regulation equal to and necessary for India's major contribution to global drug manufacture will not happen without legislators with vision who see the need for a new Drugs Act. Such an Act should have clearly drafted rules requiring rigorous and transparent evidence that supports the effectiveness and safety of new drugs in the context of public need.

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