

Need for a New Drugs Bill

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After a legislative logjam (since 2011) with respect to regulating the pharmaceuticals industry, the new government at the centre has the opportunity to introduce the much-needed changes to the Drugs and Cosmetics Act. The amendment bill, introduced in Parliament on 29 August 2013, aimed to promote rational regulation of safe and effective allopathic drugs. That bill would have been yet another patch on an Act which has already been stretched beyond breaking point. It would have done little to provide a rigorous foundation for putting safety, effectiveness, rationality and need at the heart of the country's drug regulatory system. It is to be hoped that the government will make a complete overhaul of the Act one of its highest priorities.

1 Background

Following the scathing criticisms in 2012 of a parliamentary committee (59th report),¹ India's central drugs regulator, the Central Drugs Standard Control Organisation (CDSCO) headed by the Drugs Controller General of India (DCGI),² was threatened with abolition and replacement by a central drugs authority (CDA), in the Drugs and Cosmetics (Amendment) Bill introduced in Parliament on 29 August 2013.³ The CDSCO was criticised in the 59th report for its pro-industry mission to "meet the aspirations...demands and requirements of the pharmaceutical industry"; for its apparently close cooperation with pharmaceutical companies in easing drug approvals and in avoiding legal requirements; for approving drugs without clinical trials, especially on Indian subjects; and for not exercising statutory powers to require licence revocation or drug bans. The committee also stated that "a very large number" of fixed dose combination (FDC) drugs – formulations comprising two or more drugs combined in a fixed ratio of doses and available in a single dosage form – had been approved by state regulatory authorities without prior central approval. FDCs are a peculiar feature of the Indian pharmaceutical market, compared to those on sale in England, the US or Australia.⁴

The Drugs Act of 1940 emerged from the Chopra Commission Report of 1931, on the need for central drug control legislation with a view to securing uniformity throughout the country to control the import, manufacture and sale of drugs. It remains the core primary legislation regulating drugs in India today.⁵ It divided responsibilities between the central government (responsible for import) and the provinces or (today) states (responsible for manufacture, distribution and sale). Many amendments to the Act and the Rules have been introduced, often increasing central control.⁶ In 1952, the Rules introduced the concept of a "new

drug", requiring applicants to have the written permission of the central licensing authority prior to import.⁷ In June 1961 the Rules were further amended to prohibit the manufacture of a new drug unless it had been previously approved by the central regulator;⁸ to require the manufacturer of a new drug when applying for that approval to produce all documentary and other evidence relating to its standards of quality, purity and strength "and such other information as may be required including the results of therapeutic trials carried out with it"; and to require applicants for manufacturing licences to produce evidence to the state regulator that the new drug had already been approved.⁹ These provisions were amongst the first which gave the central government increased control in relation to manufacturing; others included the powers of the central government to give directions to the states (1960);¹⁰ and to regulate, restrict and/or prohibit drugs on specified grounds in the public interest (1982 and 2008).¹¹

Nonetheless, several lacunae remain: (a) The need for a pre-approval duty on the regulator to be satisfied of the safety, efficacy and effectiveness of new drugs; (b) The requirement for accountability and transparency in the submission of clinical trial results and data; and (c) The need to address the particular challenges posed by drugs supplied in fixed dose combinations.

We address these issues and then turn to an analysis of the proposed Act in the light of these requirements.

2 'Efficacy' and 'Effectiveness'

The Act does not currently place on the central or state regulators a duty to be satisfied as to the safety and effectiveness of a drug before marketing. Such a duty does appear in the Rules, which includes a duty on regulators to be satisfied as to the safety and effectiveness of new drugs including FDCs. Surprisingly, the new long title proposed by the 2013 bill referred to efficacy. This apparently random interchangeability of the different concepts of "efficacy" and "effectiveness", and the mismatch with the regulator's duty, is not appropriate. The Cochrane Collaboration defines efficacy

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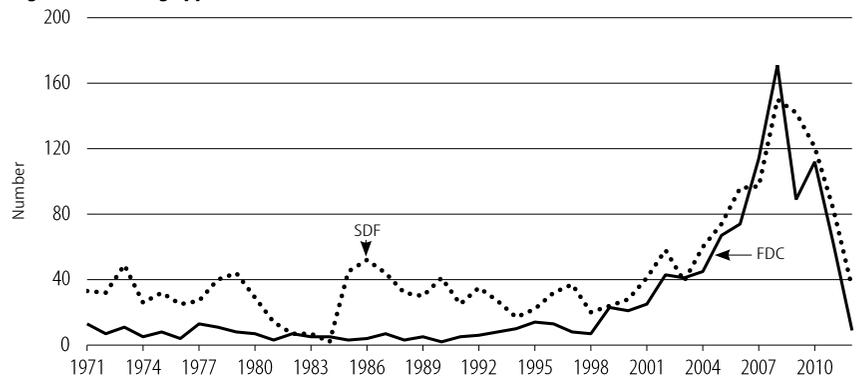
as “[t]he extent to which an intervention produces a beneficial result under ideal conditions”, and effectiveness as “[t]he extent to which a specific intervention, when used under ordinary circumstances, does what it is intended to do”.¹² Whereas in Europe or North America, the gap between efficacy and effectiveness may be mostly “a problem of variability in drug response”, in India the likelihood of off-label or inappropriate prescribing may be more important.¹³ India did not impose a safety duty until 2001, then opting for effectiveness rather than efficacy, and then only in the Drug Rules and not in the Act. There is, then, an urgent need for a new Drugs Act to clarify the criteria by which new drugs are to be judged, to include both efficacy and effectiveness.

3 Clinical Trials

Since 1988,¹⁴ the general legal position has been that clinical trials must be conducted for all “new drug substances” – from phase I onwards if they are “discovered” in India; phase III trials are necessary if they are “discovered in other countries”.¹⁵ This marked a shift in emphasis in favour of mandatory clinical trials and submission of results, with discretionary regulatory override. In 1988, minimum numbers or ranges for trial subjects were set out for different trial phases: 10-12 patients (phase II); at least 100 patients to confirm efficacy and safety in Indian patients where already approved or marketed in other countries, or at least 500 patients if discovered in India and not marketed elsewhere (phase III); plus adverse reaction data from 1,000-2,000 patients (post-marketing/phase IV). These numbers were removed by amendments in 2005.

Number ranges for trial sites were also stated in 1988: three to four centres (phase II); and three to four centres where the drug has already been approved or marketed in other countries, or 10-15 centres if discovered in India and not marketed elsewhere (phase III). These numbers were also removed in 2005. Worryingly, the actual language used in the 1988 and 2005 versions of the Rules (Schedule Y) as regards trial numbers

Figure 1: New Drug Approvals, India (1971-2012)



Data source: CDSCO. SDF: single dose formulations; FDC: fixed dose combinations.

and sites shows that these are often non-mandatory, descriptive rather than prescriptive, and in the passive voice.

In 1988, the CDSCO was given the 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”).¹⁶ The Rules are silent on what constitutes public interest and the CDSCO is still not obliged to explain or make public its reasoning when exercising this power. In 2005 an additional discretionary override on data submission was introduced, focusing on the seriousness and relevance to India of the diseases the new drugs were aimed at treating (“the disease override”).¹⁷ Again no accountability mechanisms are specified, and the 59th report (paragraph 7.17) expressly criticised the exercise of these discretions, particularly as regards the lack of trials on Indian subjects.

4 Challenges of FDCs

Official concern about FDCs dates back over 30 years.¹⁸ Provisions regulating them were first introduced into the Rules in 1988, and amended several times, particularly in 2001 and in 2005.¹⁹ Here we focus on four aspects: numbers of approvals, scope, data submission and comparison with World Health Organisation (WHO) guidelines.

(a) CDSCO Approvals: We analysed new drug approvals in India over a 42-year period from 1971-2012 using the CDSCO data (Figure 1).²⁰

During this period, 2,972 approvals were granted, 1,874 (63.1%) for single dose formulations (SDFs) and 1,098 (36.9%) for FDCs. Annual approval numbers for both SDFs and FDCs rose dramatically after 2004, and suddenly dropped in 2012 with only 35 SDFs and nine FDCs approved, and this trend appears to have continued in 2013. Why was there this sudden spurt? There is no direct reason why the 2005 Patents Act should have caused such a change, so we analysed changes in the legal drug regulatory framework.

(b) Scope: In 1988, although badly drafted, Rule 122D seems to have provided that applications for permission to import or manufacture “fixed dose combinations of drugs *already approved as individual drugs*” (emphasis added) had to be made to CDSCO, accompanied by data submission requirements. Two types of FDCs were included within the definition of a “new drug” in Rule 122E(C), namely, those “individually approved earlier for certain claims, which are now proposed to be combined for the first time [either] in a fixed ratio, or if the ratio of ingredients in an already marketed combination is proposed to be changed, with certain claims, viz, indications, dosage, form (including sustained release dosage form) and route of administration.”

Thus, on the basis of these Rules, only FDCs already approved as individual drugs which were to be combined for the first time, or where the ratio of ingredients was to change, were (and still are) within the scope of the Rules relating to new drugs. Appendix VI of the Rules,

however, includes four types of FDC, none of which require the active ingredients to have been individually approved previously:

- Type 1: those where one or more ingredient is a new drug;
- Type 2: those where the active ingredients were “already approved/marketed individually” and 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;
- Type 3: those which are “already marketed”, but where it is proposed either to change the ratio of active ingredients or to make a new therapeutic claim; and
- Type 4: those where the individual active ingredients have been “widely used in particular indication for years”, their concomitant use is often necessary, 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 (“the convenience FDCs”).

Type 4 was widened in 2005 to cover additionally those where the individual active ingredients “or drugs from the same class” have been widely used in a particular indication(s) for years.

(c) Data Submission: The four FDC types in Appendix VI have different data submission provisions. As well as extending the scope of the convenience FDC type, the 2005 amendments:

- Downgraded requirements for Type 1 FDCs from the “same” to “similar” as for other new drugs, losing the clarity of the 1988 version and replacing it with an ambiguous term, whilst erroneously but perhaps tellingly describing these requirements as “marketing data”.
- Omitted the reference to Indian trials for Type 2 FDCs and omitted any reference to any trials for Type 3 FDCs, signalling less emphasis on the need to conduct them. This is of particular concern in the case of Type 2 FDCs, as this category purports to apply to FDCs where significant pharmacodynamic or pharmacokinetic interactions are considered likely.

It is also legally doubtful whether these data submission provisions (in

Schedule X, Appendix VI) can qualify or even disapply the requirements to conduct clinical trials for “new drug substances” set out in Schedule X, Section 1(iv). Data submission provisions are, conceptually, additional to and separate from the requirement to conduct clinical trials. Applying the concept of “discovery” to FDCs, however, is not straightforward.

The CDSCO does not publish a list of FDC approvals by type, does not disclose the evidential basis for its decisions, and does not disclose unsuccessful applications. It is therefore not possible to analyse which data submission provisions were applied to which FDC applications, how the data were interpreted, or whether the public interest or disease overrides were applied.

(d) Comparison with WHO Guidelines:

WHO Guidelines post-dated the 2005 amendments, and show three noteworthy differences.²¹ First, WHO FDC types are grouped under four “scenarios”, based on whether the safety and efficacy of the active ingredients has already been established. This contrasts with the Indian FDC types in several respects, most notably as regards Types 2 and 4 which turn on substantive factors, namely, the (un)likelihood of significant pharmacodynamic or pharmacokinetic interactions, and convenience. Broadly, Indian FDC Type 1 corresponds with WHO Scenario 4; Types 2 and 3 appear 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 – the convenience FDCs – has no WHO equivalent.

Second, the WHO Guidelines suggest identifying the advantages and disadvantages of an FDC and the evidence for each considered and weighed, and that this should be part of the applicant’s submission. They also distinguish between positive scientific and medical factors, and positive cost and procurement factors for less developed countries, advising that the latter “alone are not sufficient reason to approve an FDC if it has not been justified by appropriate data and on scientific and medical

principles”. The Indian Rules adopt a different approach. Moreover, in elevating “convenience” as one of the bases for Type 4 FDCs, they are inconsistent with WHO guidelines, which list convenience as one of many factors to be weighed.

Third, as regards clinical safety and efficacy data, the WHO guidelines suggest that these should be submitted for FDCs in scenarios 3 and 4, but “not usually” for FDCs in scenarios 1 and 2. Each application should be considered on its merits using scientific judgment and logical argument. This can be contrasted with India’s Types 2 and 3, where the 2005 amendments to Appendix VI appear to be seeking to qualify, and even disapply, the requirements in Section 1(iv) of Schedule X to conduct clinical trials.

5 The New Bill

The Drugs and Cosmetics (Amendment) Bill was introduced in the Rajya Sabha on 29 August 2013. The limited bill would not have replaced the 1940 Act, and would not have imposed a duty on the regulator to ensure safety and effectiveness. The CDSCO would have been replaced by a new 20-member CDA, with regulatory powers. The bill would have retained the DCGI as the central licensing authority and designated him or her as the legal representative of the new CDA responsible for its day-to-day administration. However, the CDA would have been given no purpose or objective, only functions (duties and powers). This is surprising, given the stated intention to have extended the Act to cover safety and (oddly) efficacy.

The DCGI would have had the power to issue and cancel licences and permissions for the import, export and manufacture of drugs, and the bill would have prohibited the granting of a manufacturing licence of a new drug without the prior permission of the CDA. The bill would also have given the DCGI the power to issue manufacturing licences and export certificates for 17 listed categories of drugs, such as sera, vaccines, hormones and blood products. Currently, these are amongst 16 categories of “biological and special products” and 11 categories of “other special products” listed in Schedules C and C(I) of the Rules.

Manufacturing licences for these products have long been granted by the central regulator, so it is not clear to what extent this would amount to a substantive change.

6 Interpretation and Discussion

The considerable increases in new drug approvals from 2005-11 have been accompanied by:

- The continued absence from primary legislation of a pre-approval duty on the regulator to be satisfied of the safety and effectiveness of new drugs (inserted into secondary Rules only in 2001);
- A continuing failure to take seriously the difference between a drug's "effectiveness" and its "efficacy";
- A weakening of clinical trial provisions in 2005 alongside wide regulatory discretions to override the need to submit trial results and data, unhindered by accountability or transparency mechanisms;
- Badly drafted Rules on FDCs that allow marketing of FDCs even where safety and effectiveness of their individual components have not been previously established;
- Clinical trial provisions for FDCs that were downgraded in 2005; and
- Inconsistency with WHO Guidelines.

Imprecise 1988 Rules and 2005 amendments may have laid the regulatory ground for the record number of SDF and FDC approvals from 2005-11. For each of the SDF and FDC approvals, in the interests of public confidence there is a good case for the CDSCO to publish the safety and effectiveness evidence it used to justify approval, and its reasons for exercising either of the discretionary overrides where it has done so. Additionally it should republish its list of FDC approvals by type.

The Drugs and Cosmetics (Amendment) Bill 2013 did little to address these issues, and failed to provide a rigorous foundation for putting safety, effectiveness, rationality and need at the heart of the country's drug regulatory system. The difference between efficacy and effectiveness was overlooked. In requiring new drugs to be "effective for use", the Rules undermine the need to consider effectiveness – i.e., the treatment benefit

achieved when a drug is used in "real world" clinical practice. Randomised controlled trials are typically used as the basis for marketing approval, but they generally demonstrate efficacy rather than effectiveness. This suggests that marketing approvals should, in the first instance, be provisional and should lapse after a specified and limited period of time, with a confirmed approval given only if effectiveness has been demonstrated as a result of evidence gained during the period arising from real world use of the drug. This would provide a significant incentive for post-marketing surveillance, and would be an important global advance in drug regulation.

The new government has the opportunity to make good these failures and to give the new CDA clear statutory purposes and objectives, and to introduce a safety and effectiveness duty on the regulator when approving new drugs. The manufacture of unsafe and harmful drugs should be prohibited, as well as the manufacture of unsafe or harmful cosmetics.

Instead of another "patch" on the 73-year-old, pre-Independence Act whose structural design has been stretched beyond breaking point, the new government should consider root and branch reforms to strengthen the provisions of the Drugs and Cosmetics Act from a public health perspective. The National Democratic Alliance government has apparently decided not to bring pharmaceuticals policy under the control of the Ministry of Health. Nonetheless, the new health minister, Harsh Vardhan, comes with considerable goodwill for his record as health minister in Delhi. It is to be hoped that he will make a complete overhaul of the Drugs and Cosmetics Act one of his highest priorities.

NOTES

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- 1 The Department-Related Parliamentary Standing Committee on Health and Family Welfare, 59th Report on the Functioning of the Central Drugs Standard Control Organisation, 8 May 2012. See also the 66th Report entitled "Action taken by the Government on the Recommendations/Observations Contained in the Fifty-Ninth Report on the Functioning of Central Drugs Standard Control Organisation (CDSCO)".
- 2 Unless otherwise stated, the terms DCGI and CDSCO are used interchangeably in this article.
- 3 See: <http://164.100.47.4/BillsTexts/RSBill-Texts/asintroduced/drg%20cos-EL.pdf> (accessed 4 November 2013).
- 4 Kataria B, Bhavsar V, Donga B Contemplation on approved drugs in India from 1999 through 2011, *Asian J Pharm Clin Res*, 2012; 5(3): 25-29.
- 5 It was renamed the "Drugs and Cosmetics Act 1940" in 1962.
- 6 The Drugs and Cosmetics Rules 1945, made by the Ministry of Health and Family Welfare under the Act, have been amended on many more occasions than the 1940 Act. By way of illustration, 14 amendments to the Rules were made between October 1979 and June 1982 alone.
- 7 See Rule 30A (SRO 694, No F.1-30/48-D, dated 14 April 1952). The definition of a "new drug" was changed by the Drug First Amendment Rules 1961 (SO 115, No F.1-45/58-D, dated 4 January 1961).
- 8 This requirement remains in place. Since 1988 however, a "new drug" ceases to be considered a new drug four years after its first approval, or its inclusion in the Indian Pharmacopoeia, whichever is the earlier (Rule 122E, Explanation (ii)).
- 9 See Rule 69B inserted by Rule 8 of the Drugs Third (Amendment) Rules 1961 (SO 1449, No F.1-19/59-D, dated 13 June 1961).
- 10 The Drugs Amendment Act 1960 inserted a new power into the 1940 Act, which is now section 33P: "The Central Government may give such directions to any State Government as may appear to the Central Government to be necessary for carrying into execution in the State any of the provisions of this Act or of any rule or order made there under."
- 11 The Drugs and Cosmetics (Amendment) Act 2008 amended sections 10A and 26A (previously amended in 1982). Section 26A now reads: "Without prejudice to any other provision contained in this Chapter, if the Central Government is satisfied, that the use of any drug or cosmetic is likely to involve any risk to human beings or animals or that any drug does not have the therapeutic value claimed or purported to be claimed for it or contains ingredients and in such quantity for which there is no therapeutic justification and that in the public interest it is necessary or expedient so to do, then, that Government may, by notification in the Official Gazette, regulate, restrict or prohibit the manufacture, sale or distribution of such drug or cosmetic".

- 12 The Cochrane Collaboration: Glossary – <http://www.cochrane.org/glossary/5#lettere> (accessed 4 November 2013).
- 13 Eichler, Hans-Georg, Eric Abadie, Alasdair Breckenridge, Bruno Flamion, Lars L Gustafsson, Hubert Leufkens, Malcolm Rowland, Christian K Schneider, and Brigitte Bloechl-Daum 2011, “Bridging the Efficacy-Effectiveness Gap: A Regulator’s Perspective on Addressing Variability of Drug Response”, *Nat Rev Drug Discov*, 10(7):495-506; Jeffery, Patricia, Abhijit Das, Jashodhara Dasgupta, and Roger Jeffery 2007, “Unmonitored Intrapartum Oxytocin Use in Home Deliveries: Evidence from Uttar Pradesh, India”, *Reproductive Health Matters*, 15(30): 172-78.
- 14 A new Part XA (Rules 122A, 122B, 122C, 122D and 122E) and Schedule Y were inserted into the Rules by the Drugs and Cosmetics (Eight (sic) Amendment) Rules 1988, GSR 944(E), dated 21 September 1988.
- 15 Drugs and Cosmetics Rules 1945, Schedule Y, Section 1.1, as inserted in 1988. Schedule Y was entirely replaced by the Drugs and Cosmetics (IInd Amendment) Rules 2005, GSR 32(E), dated 20 January 2005, and now appears in Schedule Y, Section 1(iv).
- 16 See Rule 122A (for imports) and Rule 122B (for manufacture).
- 17 See Schedule Y, Section 1(3): “For drugs indicated in life threatening / serious diseases or diseases of special relevance to the Indian health scenario, the toxicological and clinical data requirements may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority”.
- 18 An expert subcommittee of the statutory Drugs Consultative Committee recommended banning certain FDCs, and in 1981 directives were issued by the DCGI to state authorities requiring strict enforcement of the recommended bans (Deshpande S W, Gandhi N Drugs and Cosmetics Act, 1940 and Rules, 1945. Mumbai: Susmit Publishers, 2012, 6th Edition: 114).
- 19 In Part XA and Appendix VI of Schedule Y, inserted by the Drugs and Cosmetics (Eight (sic) Amendment) Rules 1988, made by the Ministry of Health and Family Welfare, GSR 944(E), dated 21 September 1988; by GSR 900(E), dated 12 December 2001; and by GSR 32(E), dated 20 January 2005.
- 20 CDSCO’s lists of “approved” new drugs may describe only *approvals* to manufacture, or include also *permissions* to import. The lists may only cover the former, but the terms “approval” and “permission” are used interchangeably on its website (and, confusingly, for “marketing”, a term that is not defined). In this paper, only the term “approval” is used, and no distinction is sought to be made between approvals for manufacture and permissions to import.
- 21 WHO Technical Report Series, No 929, 2005, WHO Expert Committee on Specifications for Pharmaceutical Preparations, 39th Report.