ARTICLES

The crisis in access to essential medicines in India: key issues which call for action

ANURAG BHARGAVA[1], SP KALANTRI[2]

[1]Department of Medicine, Himalayan Institute of Medical Sciences, Jolly Grant, Dehradun, Uttarakhand 248 140 INDIA [2]Department of Medicine, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Maharashtra 442 102 INDIA Corresponding author; Anurag Bhargava e-mail: anuragb17@gmail.com

Abstract

The government is planning to introduce free generic and essential medicines in public health facilities. Most people in India buy healthcare from the private sector, a compulsion that accounts for a high proportion of healthcare-related expenditure. To reduce the burden of healthcare costs, the government must improve availability and affordability of generic and essential medicines in the market. It can do so because India's large pharmaceutical industry is a major source of generic medicines worldwide.

In this article, we discuss three factors that have impeded access to generic and essential medicines: (1) mistaken notions among policymakers, prescribers and patients about branded drugs and generic drugs in India; (2) high prices of medicines due to the progressive dismantling of the system of regulation of medicine prices, and (3) a drug approval and regulatory system that allows medicines (including fixed dose combinations) of doubtful efficacy, rationale, safety and public health relevance to dominate the market at the cost of access to affordable generic and essential medicines. The consequences of ill-health and wasted expenditure on drugs raise issues of public health ethics.

Improving access to essential medicines in India is an urgent public health and ethical imperative. This should include improved public provisioning, a system of regulation of drug prices, and an evidence-based drug approval process.

Introduction

In India, a silent crisis in access to essential medicines confronts most patients who seek treatment of acute and chronic diseases. Close to 40% of Indians live on less than US $1 per day and most of them pay out of pocket for using healthcare. Out-of-pocket spending in India is over four times higher than public spending on healthcare. Unexpected illness can have a catastrophic effect on the family of the ill person: direct out-of-pocket payments could push 2.2%% of all healthcare users and one-fourth of all hospitalised patients, into poverty in a year (1,2).

In addition, most Indians pay for medicines – a key factor that can contribute to the impoverishing effect of out-of-pocket payments for healthcare. According to the World Health Organization (WHO), an estimated 649 million people in India do not have regular access to essential medicines (3). Public provision of these medicines is poor; the median availability of 30 essential medicines in six states in India varied between 0% and 30 % (4). Patients are forced to buy medicines from the private market, a compulsion that often spells calamity for those who can ill afford the twin burdens of sickness and healthcare costs.

For example, India has the largest number of patients with diabetes in the world. A study has shown that patients belonging to the low income group in urban India were spending 27% of their annual income and those in rural India 34% of their annual income on diabetes care; most of this was spent on purchase of medicines (5). A recent study calculated the expenditure incurred on outpatient treatment of community-acquired pneumonia as a proportion of the mean per capita expenditure on food (6). Urban patients spent 17.6 % of their mean per capita expenditure on food (rural patients spent 23.4%) on the medicines prescribed for community-acquired pneumonia (6). Studies have also shown that of the rising out-of-pocket expenditures on healthcare, which push an estimated 32-39 million people below the poverty line annually(1,7), more than 70% of expenditure was incurred on purchase of medicines (1,7,8).

The reality of healthcare in India is that the private sector now caters to 80% of outpatient and 60% of inpatient care (9). Patients are therefore forced to purchase medicines from the market, which functions (and is being allowed to function) in a manner antithetical to India's public health needs. Not only do public health systems fail to provide essential drugs to patients, but the Indian pharmaceutical market is flooded with overpriced medicines that are inappropriate and irrelevant to the public health needs of the country.

The lack of access to essential medicines -- 348 drugs are listed in the national list of essential medicines of India (10) -- is the result of the inadequate budgetary provision for healthcare, the lack of a comprehensive policy on medicines in India, and a weak regulatory framework which allows medicines to be produced, promoted and prescribed without assurance of their rationality, quality or reasonableness of price. To reduce healthcare costs, it is important that people are able to access medicines of assured quality that are efficacious, safe and affordable. These essential medicines must satisfy the priority healthcare needs of a majority of the population and must be available as part of a basic healthcare system (11).

Government announcement on free generic and essential medicines

Some activities in 2012 suggest that this scenario might change. In February 2012, partly as a response to the persistent demands of civil society and the recommendations of the High Level Expert Group of the Planning Commission, the government announced plans to increase the outlay for health to 2.1% of the gross domestic product by the end of the 12th Five Year Plan (2012-17). The President's speech in the budget session of 2012 referred to plans by the government to ensure "universal access to free generic essential medicines in public health institutions in a time-bound and phased manner" (12). This plan was also referred to by the Prime Minister in his 2012 Independence Day address (13). This was a welcome announcement (even if long overdue) articulated at the highest level of the government, although a year later the scheme has still not received adequate budgetary allocation to allow for its launch. If translated into reality by exercise of political will, good governance and allocation of adequate resources, it can revitalise the public health system in India.

In this article, we discuss three factors that have impeded access to affordable generic and essential medicines in India: (1) mistaken notions among policymakers, prescribers and patients about branded drugs and generic drugs, (2) high prices of medicines due to progressive dismantling of the system of regulation of medicine prices, and (3) a drug approval and regulatory system that allows medicines (and fixed dose combinations) of doubtful efficacy, rationale, safety and public health relevance to dominate the market at the cost of access to affordable generic and essential medicines.

1. Mistaken notions of 'branded' and 'generic' medicines in India

In India, confusion and misinformation about generic medicines abound. The confusion is spread across stakeholders including the public, prescribers, policymakers and pharmaceutical trading agencies.

In their 2012 addresses to the nation, the President and the Prime Minister emphasised the importance of access to generic medicines, and rightly so, because worldwide, generic medicines are being seen as an answer to soaring healthcare costs. For example, in the US, not only are six of every 10 prescriptions filled with generic medicines (14), but pharmacists are also allowed to replace branded medicines with generic ones. By contrast, in India, home of one-fifth of the world's production of generic medicines, a consumer finds it difficult to access low-cost generics. We explain this paradox by clearing the misinformation about branded and generic medicines in India.

A generic drug is defined as a "drug product that is comparable to brand/reference listed product in dosage form, strength, route of administration, quality and performance characteristics, and intended use" (15). In countries where product patent laws are in effect, the originator firm holding the patent markets the medicines under a trademarked name with no competition for a period of up to 20 years. In these countries, generic medicines are low-cost versions of the innovator product, produced by a number of manufacturers after the patent on the medicine expires. Thus generic medicines are off-patent medicines made by companies other than the originator company, and may be marketed under a trade name (branded generic) or under the international non-proprietary name, or INN (unbranded generic). For example, Paracetamol is marketed as Crocin, Calpol, or Metacin (branded generic), or simply as Paracetamol (unbranded generic). Generic versions of the original patented drug, chemically identical to the originator product, are required by law to satisfy the same standards of quality, and are similar in safety, efficacy, risks, benefits, and intended use. Sceptics often raise the issue of bioequivalence and therapeutic equivalence of generic and brand/reference products. Actually, drug products are considered bioequivalent if there is no clinically significant difference in their bioavailability (as measured by extent and rate of absorption, and maximum blood concentration) (16). Generic drugs are identical and bioequivalent to an innovator brand (17). In the case of oral drugs, if the blood concentrations of two drugs are the same, then their concentration at the site of action and their effectiveness are also considered to be the same (16). There are few cases in which two drug products with the same active ingredient in the same dose may have different bioavailability (18). In all other circumstances, generic and brand name drugs can be considered interchangeable (19). A systematic review of 38 randomised controlled trials of generic and brand named cardiovascular drugs concluded that they were clinically equivalent (20).

The term "generics" is understood differently in India. In India, there was no patent protection for medicinal products before 2005 (only processes for manufacture of medicinal products could be patented); and the term "generic medicines" was used for those medicines which were marketed under the generic name (INN). A recent term for generic medicines used by the WHO is "multi-source pharmaceutical products", which avoids the prevailing confusion between generic medicines (which can be marketed under a brand name), and the generic (non-proprietary) name of a medicine (21). In countries like the USA, prescriptions for unbranded generics predominate, while branded generics are a small part of the market -- 58% of the dispensed prescriptions were for unbranded generics compared to only nine per cent for branded generics (14).

We use the term "generic" in line with its global usage to denote medicines which are off patent. The term used in this sense would represent virtually all the drugs in the Indian pharmaceutical market, since few enjoy patent protection. In India, the basic division is therefore not between medicines under patent and off-patent medicines, but between unbranded medicines (generic in the Indian sense) and branded medicines. Branded drugs in India are actually "branded generics" which are often misunderstood by patients, or even the media, as "patented" medicines (22), which they are not.

The brand scam

Drug makers and pharmaceutical trading agencies create an impression that branded generics are vastly superior to unbranded generics (which are often procured in the public health system and are available to patients free of cost). Even medical professionals consider unbranded generics to be substandard medicines. To add to the confusion, branded generics in India have been artificially divided by academicians and policymakers into two categories: "branded" products, which apparently refer to drugs made by "reputed" companies and promoted through doctors, and so-called "branded generics", drugs apparently made by less reputed companies and promoted through retailers (23). Patients value quality, safety and cost-effectiveness of a medicine; it matters little to them whether the medicine is branded or unbranded and whether it is promoted through the retailer or the doctor. All drugs in India also have to meet the same requirements with regard to quality, irrespective of whether they are marketed under the INN or trade name, and regardless of the route of promotion.

Drug makers and pharmaceutical trading agencies aggressively promote their brand name drugs, often using dubious means (24). Each brand claims superiority over competing brands or unbranded medicines. The top 50 companies spent Rs 5,840 crore on drug promotion in a single year (25). This practice and cleverly created myths have made it difficult for patients to access low cost medicines in India. The argument that brand *A* is better than brand *B* does not hold for a number of reasons.

First, drug makers often market the same molecule under a variety of brand names and at widely differing prices. For example, Ranbaxy uses two brand names to market ciprofloxacin: Cifran (the best-selling brand) and Ciproace (the lesser-known brand). A tablet of Cifran (500 mg) costs Rs 9.90; that of Ciproace Rs 6.20 (26). Does it mean that Cifran kills bacteria faster than Ciproace does? How would Ranbaxy justify the difference in the prices of its two brand names?

Second, drug makers also market both so-called brands and branded generics. A recent study did not find any difference in quality between brands and so-called branded generics made by the same company (23), yet the difference in price is substantial.

Third, medical professionals often indicate that they trust drugs made by highly reputed companies. Their trust is misplaced because reputed companies in India often do not manufacture but only market medicines (which may range from vitamins to very expensive antibiotics). The medicines marketed by reputed companies are actually manufactured by so-called "less reputed" companies. For example, Glaxo Smith Kline (GSK) is well known for its brands such as Zevit (multivitamin with zinc), Augmentin (amoxicillin-clavulanate: an oral and parenteral antibiotic), and Esblanem (Meropenem: an antibiotic costing Rs 1,200 per gram). Little do the doctors and public know that GSK gets them manufactured by less well-known companies such as Remidex, Medreich and Hospira and merely markets these brands (information from product packages). This is true for hundreds of other companies as well.

Fourth, the companies argue that drugs promoted through chemists are cheaper than those promoted through doctors, because they do not have to offer the incentives and freebies that they routinely offer to doctors. This argument also does not hold because companies promote medicines to doctors as well as chemists (27).While doctors are offered gifts and even incentives (28), chemists are also offered bonuses on brands and hugely discounted prices on commonly used drugs (29,30). Recent studies have shown that trade margins in India for branded drugs can vary from 200% to over 1,000% (23, 30). Self-medication practices are widespread across the different socio-economic groups in India, as is the practice of over-the-counter drug dispensing. For minor ailments, consumers often do not see a doctor and prefer to medicate themselves. Blissfully unaware of the profit margins on simple antibiotics, cough syrups, painkillers or anti-histaminics, they end up paying exorbitant prices for the over-the-counter drugs they buy from local chemists (31). Abroad, generics are much cheaper than the originator product (32). Not so in India. The so-called branded generics have a printed maximum retail price which is sometimes even higher than that of so-called branded product (23).

Prescription malpractice

We wish to emphasise that the Indian pharmaceutical market is entirely a generics market, one in which a few branded generics, masquerading as innovator products, monopolise the market. There are thousands of brand name drugs in this market and patients have little access to low-cost branded or unbranded medicines. For patients to access low-cost generic drugs, it is important that drug companies reduce their profit margin, pharmacies stock and promote them and prescribers start writing them. Although the Medical Council of India's code of ethics for doctors explicitly mentions that "Every physician should, as far as possible, prescribe drugs with generic names..." (33), this practice is seldom followed.

We believe that doctors must write drugs by generic names in both public and private sectors. To begin with, public health facilities must enforce this practice because unbranded medicines are procured and dispensed in these institutions. The usual practice of patients seeking healthcare in the public health facilities being forced to buy brand name medicines from private chemists must be checked (22). The generic-name prescriptions in the private sector haven't succeeded because private pharmacies either do not stock them or the pharmacists replace low-cost drugs with expensive branded ones. Therefore the government's advice to *all* doctors to prescribe by generic name cannot be translated into practice. Also, when doctors prescribe fixed dose combinations (FDCs), they always choose brand name drugs. They argue that because FDCs have multiple ingredients, they find it difficult to prescribe them by their non-proprietary names. Prescribing by generic name in India will take root only when doctors prescribe unbranded single ingredient medicines, and take irrational FDCs off their prescriptions.

Regulatory negligence

The drug regulatory agencies in developed countries like the US, Canada, the UK and Australia promote the use of generics and highlight their therapeutic equivalence to brand name originator products. In India, most prescribers do not know there is no difference, in pharmaceutical terms, between unbranded and branded medicines, or between brands, and the drug regulatory authorities make no effort to educate them. Both doctors and patients prefer brand name drugs over generic drugs because the latter, in their eyes, are low quality and substandard -- if not counterfeit -- drugs. Patients prefer to spend on brands they can trust, and consider a company's visibility and corporate image as a proxy for authenticity and quality control.

If the government were to provide quality assurance of all medicines available in the market, then a truly competitive market for generics competing on the basis of price could emerge in India which would immensely benefit the consumer. There would be increased prescriber support for unbranded generics in India and a better performance of schemes like the *Jan Aushadhi* stores which aim at providing good quality low-priced, unbranded medicines from five public sector companies (34, 35). Our own experience of running pharmacies at secondary and tertiary care institutions, based on low cost, unbranded as well as branded, generics sourced from carefully chosen drug companies, has been very positive in terms of savings in cost to patient and patient outcomes.

Brand name medicines in India cause the cost of treatment to spiral and are also a frequent but under-reported cause of medication errors. More than 60,000 brands exist in the Indian market but there is no registry of these drugs. As a result, brand names of medicines with dissimilar therapeutic effects (look-alike or sound-alike drugs; Table 1), result in serious medication errors (36). In our clinical practice, almost every day we see dozens of patients who are unable to find the drugs their doctors have prescribed, because the brand name drugs in the prescription they carry are available at only a few select shops close to their doctor's clinic.

2. Overpricing of medicines in India: the imperative for price regulation

Price regulation has been a key element of India's pharmaceutical policy since 1970. Prices of medicines have however been rising over the past few decades due to progressive dismantling of the system of price regulation. The Drug Prices Control Order (DPCO) initially placed price limits on 348 medicines deemed essential in India, a number that shrank to just 74 drugs by 1995 (37). Most drugs required to treat diseases of public health importance were either under-represented in this list or were not represented at all (38). The list did not include vaccines, oral rehydration salts, drugs for cancer or coronary artery disease, and included very few drugs for respiratory diseases, hypertension, and diabetes (38).

Market failure

The government tried to justify its lax control over regulation of drug prices by arguing that competition alone was enough to control their prices, an expectation belied by subsequent developments. Drugs not listed in the DPCO started getting costlier, and the rise in drug prices consistently outstripped the prices of all other commodities (37). For 17 years -- 1995 to 2012 -- the number of drugs under price control did not change.

A public interest litigation filed in the Supreme Court of India is seeking to re-introduce price regulation of all the medicines in the National List of Essential Medicines (NLEM). At the behest of the court, the NLEM was recently revised (10) and a revised National Pharmaceuticals Pricing Policy is on the anvil (39).

The government, however, intends to switch to a market-based pricing formula which, if implemented, will either only marginally reduce drug prices, or may actually increase them (40,41). Several publications have pointed out that the new policy may adversely impact public health in India (42-44). An analysis of the top-selling 300 brands suggested that 62% of them contained medicines outside the NLEM, and of the 115 FDCs only 20% could be considered rational (45). These medicines and such combinations would be outside the purview of price control, and this would reduce the efficacy of price control as an intervention to reduce healthcare-related costs.

Are price differentials ethical?

Medicines are overpriced in India. In India, the pharmaceutical sector shows three types of price differentials which reflect this overpricing. The first differential is the greater than 10-fold difference in the maximum retail price of different brands of the same medicine which is seen in the market (Table 2). Differences between retail prices of perhaps a lesser magnitude are seen across therapeutic categories of medicines in India. The disconcerting fact is that in India the market leader in a particular therapeutic segment is also the price leader, or amongst the highest priced medicines in that segment. For example, Atorva, an anti-lipid brand name drug, outsells hundreds of brands, some of which are 10 times cheaper (Table 2). This is clearly an indication that market forces fail to regulate drug prices, as was naively assumed by the government over the years. This state of affairs exists because patients pay but do not decide, while doctors – the key players who are often heavily influenced by the pharmaceutical companies – decide but do not pay. In such a situation, patients with diseases like diabetes, hypertension or cancer pay substantially more if their doctor prescribes the more expensive brand for each of these conditions.

The second inexplicable difference in prices is between the price to retailer and the price to consumer for branded generics. A study found trader margins for the branded generics promoted through retailers of the order of 201-1,016% (23). These enormous trade margins have been known to the government since 1998 as pointed out by the Drug Price

Control Review Committee. This vast differential points to the enormous mark-ups which exist in drugs and which are being pocketed either by the pharmaceutical trader or the company (hospitals and doctors who dispense the drugs also share the profits). If drug makers agree to reduce the exorbitant profit margins, and drug prices are tightly regulated, all drugs might become available at affordable prices.

The final revealing differential is between the price paid for purchase of medicines in pooled public procurement programmes in Tamil Nadu and other states which buy quality assured medicines, and of the brands which sell in the market. For example, Tamil Nadu procured 10 tablets of Omeprazole (a commonly used drug for acid peptic disease) for Rs 2.4 while the market leader sells at Rs 39.7 for 10 tablets (46). Similarly, Tamil Nadu procured human insulin at nearly a third of the prevailing market price. The variation in retail prices, the margins offered to the traders, hospitals and doctors who dispense the drugs and the difference between retail prices and prices in pooled procurement are unique to the pharmaceutical sector.

These differentials raise an ethical question for public policy. These price variations may not be illegal, but are they morally right? Are these wide variations in drug prices – which have no parallel amongst all other commodities – ethically acceptable when access to medicines can constitute the difference between life and death? Should the government not intervene to ensure that patients are not at the mercy of the prescribers' whims and the vagaries of the market? Should the ambit of price regulation not cover all medicines as suggested by the National Commission of Macroeconomics and Health (37), rather than just the 348 medicines mentioned in the NLEM? Won't this control of prices, limited to those of essential medicines, induce the industry to migrate from production of price-controlled medicines to those outside control? This selective approach to price control could ultimately promote the production and marketing of medicines which are not in the NLEM.

3. The need for evidence-based drug approval and improved access to essential medicines

India and its pharmaceutical industry have acquitted themselves very creditably on the global platform. Indian generics account for about 40% of the anti-retroviral medicines provided globally. Worldwide, these low-cost high-quality medicines are a lifeline to millions of people. There are an estimated 10,563 manufacturers in India, and more than 65,000 formulations (47).

These numbers look impressive but the paradox is that, at home, "large portions of the population lack access to even the most essential drugs. The limited funds available are frequently spent on ineffective, unnecessary, or dangerous medications."(48:16.2). The money spent on overpriced medicines is very often also a waste of precious resources. This is because the Indian pharmaceutical market is full of ineffective, unnecessary medicines. Since these medicines outnumber those which are cost-effective, they directly impact the availability of and access to essential medicines (49).

Lack of essential medicines in the market

Iron deficiency anaemia is an important public health problem in India, associated with low birth weight in infants, pregnancy-related deaths, and decreased work capacity. Ferrous sulphate and ferrous fumarate – low cost medicines recommended for treatment of iron deficiency which are distributed free of cost in public health facilities – are not available in most drug stores in India. The July 2012 edition of *Current Index of Medical Specialities* (*CIMS*), a prescriber handbook, does not mention a single preparation which contains ferrous sulphate in the dose mentioned in the NLEM 2011(46). Hundreds of iron preparations are available in the market- they contain salts with poor efficacy or co-existing with other nutrients (vitamins, minerals including zinc, amino acids) which do not increase their efficacy (50). Yet they cost much more than simple iron preparations and push up the cost of treatment of iron deficiency anaemia as much as 70-fold, according to an estimate (51). We are unable to understand why such ineffective and irrational preparations continue to be in the market and why iron pills are not under price control.

Dexorange was a market leader for the treatment of iron deficiency anaemia. Although this drug contained a poorly absorbed salt of iron and haemoglobin that came from slaughterhouse blood, (52) it enjoyed a lot of support from medical professionals between 1970 and 2000 (when the use of haemoglobin in anaemia preparations was finally banned). This combination had no parallel anywhere in the world. Similarly, the market is flooded with irrational fixed dose combinations to treat infectious diseases, as well as "me-too" drugs -- members of the same group as essential medicines which do not confer any therapeutic advantage but are more expensive. It is a moot point whether the 11 calcium channel blockers available in the Indian market fulfil any therapeutic need (46). On the other hand, essential medicines are scarce. Thiazide diuretics are amongst the cornerstones of treatment of hypertension. However, there were only five brands of thiazides listed in *CIMS*, while there are 131 brands of thiazides in combination with other medicines (26).

Unnecessary and irrational fixed dose combinations

Fixed dose combinations (FDCs) are combinations of drugs, used in situations where such a combination is pharmacologically justified. More than 40% of the formulations in India are composed of FDCs (53), a proportion which is unprecedented. For example the NLEM which lists 348 medicines has only 15 combinations of medicines (10). In contrast, in the market there are more than 15 combinations of paracetamol alone.

FDCs are justified when the combination of the active drugs increases efficacy, decreases adverse effects, reduces the risk of drug resistance, lowers prescription cost, simplifies therapy or promotes adherence to therapy (21). Such combinations with a

therapeutic advantage are therefore justified (some examples are oral contraceptives, anti-malaria therapy, anti-TB drugs, HIV therapy, and drugs for asthma, hypertension and diabetes). A basic requirement is that the drugs comprising the FDC should have compatible pharmacokinetics and pharmacodynamics. The major disadvantage of FDCs is an inability to vary the dose of the individual components of the combination, and increased incidence of adverse effects (21).

In India, the FDCs often lack pharmacological justification. India's most widely available antibiotic combination of ampicillin/amoxicillin and cloxacillin is pharmacologically irrational (54), compromises the treatment of staphylococcal infections because the dose of cloxacillin in the FDC is half of what it ought to be, and promotes the development of drug resistance. The use of other FDCs of antibiotics like ciprofloxacin + metronidazole has contributed to increasing resistance in enteric infections like typhoid fever

FDCs often also contain chemicals which lack efficacy but increase the cost of therapy. For example, an FDC of painkillers with serratiopeptidase, a drug isolated from silkworm intestine, is commonly prescribed in India. This drug was voluntarily withdrawn from the market in Japan by its manufacturer Takeda in 2011, when clinical trials failed to show evidence of its efficacy compared to placebo, but continues to be popular in India (55).

A number of FDCs are downright hazardous. The European Medicines Evaluation Agency approved Nimesulide only for restricted and short term use in adults. The agency warned that combination of this drug with other painkillers like paracetamol could adversely affect the liver (56). Yet, several leading Indian companies (Lupin, IPCA, and Dr Reddy's Laboratories) market such FDCs in India.

Table 3 lists the irrational FDCs made in India. Indian pharmaceutical manufacturers have WHO good manufacturing practices certification and a number of them have US FDA approval. Is it not axiomatic that the content of medicines manufactured be also such that would stand the scrutiny of an agency outside India? The presence of unnecessary and ineffective drugs makes the process of drug regulation even more daunting as the authorities waste their time and resources fixing the prices or monitoring the quality of preparations which should not have been manufactured in the first place. For example, the National Pharmaceutical Pricing Authority has determined prices for 78 formulations of cloxacillin, a medicine which is under price control. All these 78 formulations are irrational as they contain combinations of cloxacillin with various other antibiotics (ampicillin, amoxicillin, cefixime, cefpodoxime), and varying concentration of lactobacillus spores (20-60 million) (57).

The drug approval process in India and its lacunae

Drug regulatory agencies all over the world approve medicines for use in their countries on the basis of an evidence-based process which evaluates the data on their efficacy (obtained through randomised controlled trials) and safety. In India in light of the public health problems that we face, the widespread poverty and high out-of-pocket expenditure incurred by patients, the drug regulatory authorities have an additional responsibility: to ensure that the medicines being approved for manufacture serve the public health needs of the country and are cost-effective.

The Drugs Controller General of India (DCGI) heads the Central Drug Standards Control Organization (CDSCO) which oversees the process of approval of medicines for India. This process needs to be rigourous, transparent and evidence-based, as is the case with drug regulatory agencies in the developed countries. The website of the CDSCO should list the approval letters, approved indications, and information for patients who are to use the product.

However, the drug regulatory agencies in India have paid inadequate attention to rigourous, impartial review of the scientific evidence, public health relevance, transparency and public disclosure before approving a drug. A parliamentary committee report on the functioning of the CDSCO in 2012 observed: "A review of the opinions submitted by the experts on various drugs shows that an overwhelming majority are recommendations based on personal perception without giving any hard scientific evidence or data. Such opinions are of extremely limited value and merely a formality. Still worse, there is adequate documentary evidence to come to the conclusion that many opinions were actually written by the invisible hands of drug manufacturers and experts merely obliged by putting their signatures" (58:17).

The issue of irrational FDCs in India is a pointer to the lacunae in the drug approval process. The genesis of many irrational FDCs has been at the state level where the state licensing officers in contravention of the amended Drugs and Cosmetics Act were found to be issuing licenses to companies for the manufacture of FDCs. The DCGI issued a directive in 2002 to all the state drug controllers to refrain from issuing any new drug licensing for the manufacture of FDCs (59). But as was noted by the parliamentary committee, no action has been taken in the past 11 years on this issue (58).

In response to a public interest litigation the DCGI's office had identified 294 FDCs which had been sanctioned by the state licensing authorities without its approval (60, 61). Such FDCs are illegal and could have been banned immediately, but even these have yet to be withdrawn. One example from this list of FDCs that was approved by a state licensing agency, though classified as 'absurd' by the DCGI, is a combination of non-steroidal anti-inflammatory drugs and other drugs, chlorzoxazone + Ibuprofen+Paracetamol+diclofenac+Oxyphe nbutazone+Magnesium hydroxide (61).

While state drug controllers can be blamed for many irrational FDCs, irrational FDCs have been approved in recent years by the CDSCO. FDCs of antibiotics are clearly dangerous to public health – as pointed out in the recent parliamentary committee report. For example, the DCGI has approved an

FDC of Moxifloxacin with cefixime for the treatment of lower respiratory tract infections (Table 3). Moxifloxacin is a newer generation fluoroquinolone and one of the few orally effective drugs for multi-drug resistant tuberculosis. Such a combination, if used frequently to treat pneumonia, could further complicate the problem of multi-drug resistant TB.

Need for transparency in the approval process

In its report, the parliamentary committee drew attention to a "collusive nexus between drug manufacturers, some CDSCO functionaries and some medical experts" (58:20) which resulted in irregular drug approvals. On the issue of irrational FDCs, it stated in very clear terms, "The Committee is of the view that Section 26A is adequate to deal with the problem of irrational and/or FDCs not cleared by CDSCO. There is a need to make the process of approving and banning FDCs more transparent and fair. In general, if an FDC is not approved anywhere in the world, it may not be cleared for use in India unless there is a specific disease or disorder prevalent in India, or a very specific reason backed by scientific evidence and irrefutable data applicable specifically to India that justifies the approval of a particular FDC. The Committee strongly recommends that a clear, transparent policy may be framed for approving FDCs based on scientific principles" (58:27).

Irrational FDCs continue to thrive because drug companies take advantage of the lengthy litigation in Indian courts. In such cases the onus of proof – that the FDCs are harmful– lies on the complainant. With virtually no system of post-marketing surveillance, it is nearly impossible to gather evidences of harm against FDCs in India.

Lessons from successful initiatives in improving access to essential medicines

As the government endeavours to improve the availability of medicines in public health facilities, it would be beneficial for it to incorporate lessons from some successful initiatives in improving availability of essential medicines. Beginning October 2, 2011, Rajasthan state has started supplying free medicines at public health facilities. Since 1994, Tamil Nadu Medical Services Corporation has ensured ready availability of all essential drugs and medicines in the government medical institutions throughout Tamil Nadu by adopting a streamlined and transparent procedure for their procurement, storage and distribution. This quality-assured process of pooled public procurement has several features worthy of replication at the national level (62,63). A similar initiative has been implemented in Delhi state (64).

These initiatives have succeeded in procurement of unbranded essential medicines at very low prices, eliminating irrational medicines and unscientific fixed dose combinations. They have shown that given political and administrative will, it is not difficult to gather support from healthcare professionals for improving access to healthcare and decreasing the burden of expenses for patients, while achieving substantial savings in cost for the public exchequer.

The common people who purchase medicines at nearly half a million chemist shops in India, every day, await a similar exercise of political and administrative will of the government to improve access to low-cost drugs in the public health facilities. As this article goes to press, the quantum of funds for the free generic medicines scheme is not known as it did not appear in any line item in the budget for 2013-2014.The Working Group on Food and Drugs Regulations for the 12th Plan has estimated that an allocation of just Rs 5,000 crore per year would suffice to fulfil the central government's share (85%) of the cost of the 'free medicines for all' scheme (65).

Direct out-of-pocket payments push one out of 45 healthcare users into poverty in a year; this number would fall to just one of 200 if healthcare users do not have to pay out-of-pocket for purchase of medicines (2). Reduction of this out-of-pocket spending on medicines which is impoverishing people by the millions is an ethical imperative for public health in India.

In conclusion, the plan to improve access to essential medicines through improved provisioning in public health facilities is a welcome initiative. However, given the current realities of the healthcare system in India and the catastrophic effects of out-of-pocket payment on purchase of medicines being borne by the poor, making essential and rational medicines affordable in India is also an urgent imperative.

The government must correct the present distortions around the concept of generic medicines in India by providing quality assurance of medicines, emphasising the equivalence of different branded or unbranded medicines, and allowing the emergence of a true generics market, where different products can compete on price rather than on brand image. Prescription by generic name in all public health facilities should be mandated. The market should be made to move towards single ingredient, unbranded medicines.

To address the anarchy of drug prices which is impoverishing people, we need a comprehensive cost-based system, and not the market-based system of price regulation. The drug approval system in India needs to be overhauled on the lines suggested by the recent parliamentary committee which looked into the functioning of the CDSCO (58). The process of drug approval needs to be rigourous, evidence-based, transparent, and in line with the interests of public health in India. The government should address the lack of single-ingredient essential medicines in India for priority health conditions. All FDCs which lack a pharmacological rationale, contain ineffective or hazardous combinations, or are illegally approved by state drug controllers need to be removed from the market. The present predicament, of poverty of access to medicines amidst a plenty of overpriced, non-essential medicines which worsen poverty, should not be allowed to continue to imperil the lives and health of Indians.

Disclaimer: *Anurag Bhargava contributed to this article in his personal capacity. The views expressed are his own and do not necessarily represent the views of the Himalayan Institute of Medical Sciences or HIHT University.*

Table 1: Look alike and sound alike brands in India			
Brand name	**Composition**	**Manufacturer**	**Use**
LONA	Low sodium salt	Dabur	For use in hypertension, heart failure
Lona	Clonazepam	Triton Healthcare	In epilepsy
AZ	Albendazole	Cure Quick Pharma	Worm infestation
AZA	Vitamin C, Lycopene, Vitamin A, Zinc, Selenium	Moraceae	Vitamin and mineral supplement
AZZA	Azithromycin	Wintech	Antibiotic
Clopin	Clozapine	East West	Antipsychotic
Clopione	Clopidogrel	Wockhardt	Antiplatelet drug

Source: CIMS July 2012, company websites

Table 2: Overpricing in medicines in India					
Name of drug	**Use**	**Unit**	**Lower priced generic**	**Highest priced generic**	**MGIMS Sevagram Price (2012)**
Risperidone 1 mg tablets	Psychosis	10 tablets	Sizomax (RPG)Rs 14	Risperdal [J&J (Ethnor)] Rs 135	Rs 135Riz (Alkem Lab)Rs 13.90
Amlodipine 5 mg tablets	Hypertension	10 tablets	Amlibon (Novartis) Rs 15	Amlogard (Pfizer) Rs 79	Biodepine (Biochem Pharma) Rs 4.40
Enalapril 5 mg tablets	Hypertension	10 tablets	Myoace (Merck) Rs 16.75	Envas (Cadila)Rs 46.07	Encardil (Medley) Rs 24.75
Atenolol 50 mg tablets	Hypertension	14 tablets	Ziblok (FDC)Rs 8.00	Tenormin (Nicholas)Rs 43.96	Ziblok (FDC) Rs 7.70
Ramipril 2.5 mg tablets	Cardiac failure	10 tablets	Sclerace (Novartis) Rs 29	Cardace (Sanofi Aventis) Rs 73	Odopril (Blue Cross)Rs 20.70
Tamoxifen 10 mg tablets	Breast cancer	10 tablets	Oncomox (Sun)Rs 15.50	Nolvadex(Astra Zeneca)Rs 186	Cytotam (Cipla)Rs 11.40
Letrozole 2.5 mg tablets	Breast cancer	10 tablets	Oncolet (Biochem)Rs 99	Femara (Novartis)Rs 1,815	Letrofil (Fortus) Rs 320.45
Atorvastatin 10 mg tablets	High cholesterol	10 tablets	GenXvast (Hetero)Rs 10	Atorva (Zydus)Rs 104	Stator (Abbott) Rs 8.80
Ciprofloxacin 500 mg tablets	Antibiotic	10 tablets	Zoxan (FDC)Rs 49	Cifran (Ranbaxy)Rs 99	Swiflox (Indswift)Rs 18.40
Glimepiride 2 mg tablets	Antidiabetic	10 tablets	K-Glim (KAPL)Rs 15	Amaryl (Sanofi Aventis) Rs117.40	K-Glim (KAPL) Rs 14.70
Ceftriaxone 1 g Inj.	Antidiabetic	vial	Eracef (Brawn) Rs 42.50	Nosocef (Merind) Rs 179	C-One (Abbott) Rs 19.22
PiperacillinTazobactum 4.5 g Inj.	Antidiabetic	vial	Pirotaz (Samarth)Rs 280	Zosyn (Wyeth)Rs 967	Tazira (Piramal Heathcare) Rs 138
Streptokinase 1.5 million units Inj.	Cardiac	vial	Indikinase (Bharat Biotech)Rs 1,500	Streptonase (United Biotech)Rs 3,450	Glanikinase (GlandPharma) Rs 756
Enoxaparin 60 mg Inj.	Cardiac	vial	Enclex (Cipla) Rs 238	Clexane (Sanofi Aventis) Rs 615	Troynoxa (Troikaa)Rs 153
Cisplatin 50 mg Inj.	Anti-cancer	vial	Plationco injection (Chandra Bhagat) Rs 31	Blastolem (Elder) Rs 511.98	Oncoplatin (Sun Pharma) Rs 47.88

Source: CIMS India, April-July 2012, www.medlineindia.com. Mahatma Gandhi Institute of Medical Sciences pharmacy rate list (December 2012)

Table 3: Fixed dose combinations approved by DCGI, to be 'made only in India'	
Fixed dose combination	**Indication for use**
Amoxicillin 250 mg + Cloxacillin 250 mg + Lactobacillus spores	Infections
Cefixime 100mg + Cloxacillin (as Sodium) 500mg + Lactobacillus (45 million spore)tab	Antibiotic
Metformin + Alpha lipoic acid	Diabetic polyneuropathy
Enalapril + Hydrochlorthiazide+ Paracetamol	Hypertension
Ceftazidime 500 mg + Tobramycin 60 mg injection	Infections with Pseudomonas aeruginosa
Cefixime 100/200 mg + Cloxacillin250 mg	Upper and lower respiratory infections
Alpha Lipoic Acid USP 100mg + Methylcobalamin 1500mcg + Vitamin B6 IP 3mg + Folic Acid IP 1.5mg + Benfotiamine 50mg + Biotin USP 5mg + Chromium Picolinate USP Eq. to Chromium 200mcg Capsule	Treatment of diabetic polyneuropathy
Cefixime (SR) 400mg +Moxifloxacin (SR) 400 mg Tablets	For the treatment of lower respiratory tract infections in adults only
Nitazoxanide + Ofloxacin	Urogenital infection
Vitamin C 500 mcg+ Zinc citrate 2.2 mg+ Selenium 60 mcg	For Vitamin C deficiency

Source: http://cdsco.nic.in for list of approved drugs for 2006-2011. [cited 2013 Feb 3]

References

1. van Doorslaer E, O'Donnell O, Rannan-Eliya RP, Somanathan A, Adhikari SR, Garg CC, Harbianto D, Herrin AN, Huq MN, Ibragimova S, Karan A, Ng C, Pande BR, Racelis R, Tao S, Tin K, Tisayaticom K, Trisnantoro L, Vasavid C, Zhao Y. Effect of payments for health care on poverty estimates in 11 countries in Asia: an analysis of household survey data. *Lancet*. 2006 Oct 14;368 (9544):1357-64.
2. Shahrawat R, Rao KD. Insured yet vulnerable: out-of-pocket payments and India's poor. *Health Policy Plan*. 2012 May;27(3):213-21.
3. World Health Organisation. *The world medicines situation*[Internet]. Geneva: WHO;2004[cited 2013 Mar 25]. Chapter 7, Access to essential medicines;p.63. Available from: http://apps.who.int/medicinedocs/pdf/s6160e/s6160e.pdf
4. Kotwani A, Ewen M, Dey D, Iyer S, Lakshmi PK, Patel A, Raman K, Singhal GL, Thawani V, Tripathi S, Laing R. Prices & availability of common medicines at six sites in India using a standard methodology. *Indian J Med Res*. 2007 May;125(5):645-54.
5. Ramachandran A, Ramachandran S, Snehalatha C, Augustine C, Murugesan N, Viswanathan V, Kapur A, Williams R. Increasing expenditure on health care incurred by diabetic subjects in a developing country: a study from India. *Diabetes Care*. 2007 Feb;30(2):252-6.
6. Roy V, Gupta U, Agarwal AK. Cost of medicines & their affordability in private pharmacies in Delhi (India). *Indian J Med Res*. 2012 Nov;136 (5):827-35.
7. Garg CC, Karan AK. Reducing out-of-pocket expenditures to reduce poverty: a disaggregated analysis at rural-urban and state level in India. *Health Policy Plan*. 2009 Mar;24 (2):116-28.
8. Peters DH, Yazbeck AS, Sharma RR, Ramana GNV, Pritchett LH, Wagstaff A, editors. *Better health systems for India's poor: findings, analysis and options*. Washington DC: World Bank; 2002.347p.
9. Selvaraj S, Karan AK. Deepening health insecurity in India: evidence from National Sample Surveys since 1980s.*Econ Pol Wkly*. 2009;44 (40):55-60.
10. Ministry of Health and Family Welfare, Government of India. *National List of Essential Medicines of India* [Internet]. New Delhi: MoHFW, GoI; 2011[cited 2013 Mar 22]. Available from: http://cdsco.nic.in/National%20List%20of%20Essential%20Medicine-%20final%20copy.pdf
11. Quick JD, Hogerzeil HV, Velasquez G, Rago L. Twenty-five years of essential medicines. *Bull World Health Organ*. 2002;80 (11):913-4.
12. President Pratibha Patil's address to Parliament [Internet].*The Hindu* [Online Ed]. 2012 Mar 12[cited 2013 Mar 25][about 10 screens]. Available from: http://www.thehindu.com/news/resources/article2987867.ece
13. Dr Manmohan Singh, Prime Minister of India [Internet]. New Delhi: Government of India. PM's Independence Day Speech, 2012;2012 Aug 15[cited 2013 Apr 8]; [about 2 screens].Available from: http://pmindia.gov.in/speech-details.php?nodeid=1199.
14. Generic Pharmaceutical Association. *Annual report 2008 —Generics: the right choice for better health* [Internet]. Arlington, VA: Generic Pharmaceutical Association; 2008[cited 2013 Mar 23]. Available from: http://members.gphaonline.org/AM/Template.cfm?Section=Home&Template=/CM/ContentDisplay.cfm&ContentID=4201
15. Center for Drug Evaluation and Research. *Generic drugs* [Internet]. Maryland, USA: US Food and Drug Administration; 2010[cited 2013 Apr 8]. Available from: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm127615.pdf
16. Canadian agency for drugs and technologies in health. What are bioavailability and bioequivalence?[Internet].Ontario, Canada: CADTH; 2012 [cited 2013 Apr 8]; 3p.Available from: http://www.cadth.ca/media/pdf/Generic_prof_supplement_en.pdf
17. US Food and Drug Administration. Generic drugs: Questions and Answers[Internet]. Maryland, USA:US FDA;2011[cited 2013 Apr 8] [about 2 screens]. Available from: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm100100.htm.
18. Meredith P. Bioequivalence and other unresolved issues in generic drug substitution. *Clin Ther*. 2003 Nov;25(11):2875-90.
19. Kesselheim AS. The backlash against bioequivalence and the interchangeability of brand-name and generic drugs. *CMAJ*. 2011 Sep 6;183(12):1350-1.
20. Kesselheim AS, MR, Brookhart MA, Choudhry NK, Shrank WH.. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. JAMA. 2008 Dec 3;300(21):2514-26.
21. World Health Organization. *WHO expert committee on specifications for pharmaceutical products : thirty-ninth report*. Geneva: WHO; 2004[cited 2013 Mar 23].Available from: http://apps.who.int/prequal/info_general/documents/TRS929/WHO_TRS_929_annex5FDCs.pdf
22. Mani R. Doctors not prescribing generic drugs [Internet]. *The Times of India* [Online Ed]. 2009 Feb 3[cited 2013 Mar 25][about 3 screens]. Available from: http://articles.timesofindia.indiatimes.com/2009-02-03/allahabad/28005062_1_generic-drugs-generic-medicines-patent-drugs
23. Singal GL, Nanda A, Kotwani A. A comparative evaluation of price and quality of some branded versus branded-generic medicines of the same manufacturer in India. *Indian J Pharmacol*. 2011 Apr;43 (2):131-6.
24. Gulhati CM. Marketing of medicines in India.*BMJ*. 2004 Apr 3;328 (7443):778-9.
25. Soneji H, Banerjee A. Indian pharma majors prefer brand promotion over R&D[Internet]. *Economic Times*. 2004 Dec15[cited 2013 Mar 23]. Available from: http://articles.economictimes.indiatimes.com/2004-12-15/news/27417728_1_indian-pharma-r-d-pharma-companies
26. *Current Index of Medical Specialities*. Bangalore: UBM Medica India Ltd; 2012;117 (2):277.
27. Roy N, Madhiwalla N, Pai SA. Drug promotional practices in Mumbai: a qualitative study. *Indian J Med Ethics*. 2007 Apr-Jun;4 (2):57-61.
28. Lodha R, Bhargava A. Financial incentives and the prescription of newer vaccines by doctors in India. *Indian J Med Ethics*. 2010 Jan-Mar;7 (1):28-30.
29. Pearl D, Steckelow S. Drug firms' incentives fuel abuse by pharmacists in India. *Wall Street Journal*[Internet]. 2001 Aug 16[cited 2013 Mar 23]. Available from: http://online.wsj.com/article/SB997910373349012375.html
30. Lalwani H, Kotkar S. *Study of incentives being provided by medical companies to retailers*. Mumbai: IIT Mumbai; 2011.
31. Lal V, Goswami A, Anand K. Self-medication among residents of urban resettlement colony, New Delhi. *Indian J Public Health*. 2007 Oct-Dec;51 (4):249-51.
32. Anis A, Harvard S, Marra C. Ontario's plunging price-caps on generics: deeper dives may drown some drugs. *Open Med*. 2011;5 (3):e149-52.
33. Medical Council of India. *Indian Medical Council (Professional Conduct, Etiquette, Ethics) regulations 2002* [Internet]. New Delhi: Medical Council of India; 2002 Mar 11[cited 2013 Mar 25].8p. Available from: . http://www.mciindia.org/RulesandRegulations/CodeofMedicalEthicsRegulations2002.aspx
34. Jha DN. What ails the generic drug?[Internet] *The Times of India*. 2012 July 29[cited 2013 Mar 23]. Available from: http://articles.timesofindia.indiatimes.com/2012-07-29/special-report/32923254_1_generic-drugs-quality-and-efficacy-pioneer-drug
35. Jayaraman K. Troubles beset 'Jan Aushadhi' plan to broaden access to generics. *Nat Med*. 2010 Apr;16 (4):350.
36. Rataboli PV, Garg A. Confusing brand names: nightmare of medical profession. *J Postgrad Med*. 2005 Jan-Mar;51 (1):13-6.
37. National Commission on Macroeconomics and Health, Government of India. *Report of the National Commission on Macroeconomics and Health*. New Delhi: National Commission On Macroeconomics And Health, MoHFW, GoI; 2005.
38. Bhargava A. Price control policy and public health: irrelevance and danger of applying only economic criteria. In: Srinivasan S, Bhargava A, editors. *Impoverishing the poor: pharmaceuticals and drug pricing in India*. Vadodara/Bilaspur: LOCOST/Jan Swasthya Sahyog; 2004. p. 105-9.
39. Government of India. *Draft National Pharmaceutical Pricing Policy*[Internet].New Delhi: Department of Pharmaceuticals Ministry of Chemicals and Fertilisers;2011[cited 2013 Mar 25]. Available from: http://pharmaceuticals.gov.in/mshT2810/FTY2.pdf
40. Perapaddan BS. Concern over market based mechanism to control drug prices. *The Hindu*[Internet]. 2012, Oct 3[cited 2013 Mar 23]. Available from: http://www.thehindu.com/todays-paper/tp-national/tp-newdelhi/concern-over-marketbased-mechanism-to-control-drug-prices/article3959922.ece

41. Vaidyanathan G. Poor may suffer as India caps drug prices. *Nature* [Internet]. 2012 [cited 2013 Mar 25] [about 5 screens]. Available from: http://www.nature.com/news/poor-may-suffer-as-india-caps-drug-prices-1.12046.
42. Selvaraj S, Hasan H, Chokshi M, Sengupta A, Guha A, Shiva M, et al. Pharmaceutical pricing policy: a critique. *Econ Pol Wkly*. 2012;47 (4):20-3.
43. Selvaraj S, Farooqui HH. Draft Drug Price Policy 2011: Legitimising unaffordable medicine prices? *Econ Pol Wkly*. 2012;47 (46):13-7.
44. Srinivasan S, Phadke A. Pharma policy 2012 and its discontents. *Econ Pol Wkly*. 2013;48 (1):38-42.
45. Bhargava A. Anomalies in Drug Pricing and Sale of Drugs. In: Srinivasan S, Bhargava A, editors. *Impoverishing the poor: pharmaceuticals and drug pricing in India*. 2nd ed. Vadodara/Bilaspur: LOCOST/JSS; 2004. p.125-38.
46. *Current Index of Medical Specialities*. 2012;117 (2).
47. Annual Report 2010-11. New Delhi: Department of Pharmaceuticals Ministry of Chemicals and Fertilisers, Government of India 2011.
48. Management Sciences for Health [Internet]. Massachusetts, USA: MSH; c 1999-2009. MDS-3: Managing Access to Medicines and Technologies;2012[cited 2013 Apr 8]. p.16. Available from: www.msh.org/resource-center/managing-drug-supply.cfm
49. Bhargava A. Dubious rather than spurious drugs: India's real drug problem. *Health Action*. 2009 (September):4-7.
50. Karelia BN, Buch JG. Analysis of hematinic formulations available in the Indian market. . J Pharmacol Pharmacother. 2012 Jan;3(1):35-8.
51. Bhargava A. Drug costs in treatment of common and important illnesses and affordability of treatment costs. In: Srinivasan S, Bhargava A, editors. *Impoverishing the poor: Pharmaceuticals and drug pricing in India*. Vadodara/Bilaspur: LOCOST/Jan Swasthya Sahyog; 2004. p. 94-5.
52. Menon S. From buffalo's veins to the medicine chest[Internet]. *Indian Express*[Online Ed]. 1999 September 20[cited 2013 Mar 25]. Available from: http://expressindia.indianexpress.com/news/ie/daily/19990921/ige21073.html
53. Gulhati CM. Generics: Why, which and for whom? *Monthly Index of Medical Specialities*.2012 Aug.
54. Gautam CS, Saha L. Fixed dose drug combinations (FDCs): rational or irrational: a view point. *Br J Clin Pharmacol*. 2008 May;65 (5):795-6.
55. Health Science Authority, Singapore. *HSA updates on the phasing-out of serratiopeptidase-containing preparations as medicinal products*[Internet]. Singapore:2011[cited 2013 Mar 25].[about 2 screens].Available from: http://www.hsa.gov.sg/publish/hsaportal/en/news_events/hsa_updates/2011/hsa_updates_on_the0.html?CFC_cK=1322548580121.
56. European Medicines Evaluation Agency. Amendments to be included in the relevant sections of the summary of product characteristics of nimesulide containing medicinal products (systemic formulations). 2010; Available from: http://www.emea.europa.eu/pdfs/general/direct/pr/nimesulide_annexIII.pdf
57. National Pharmaceutical Pricing Authority [Internet]. New Delhi: Department of Pharmaceuticals, Ministry of Chemicals and Fertilizers,Government of India. CEILING PRICES Scheduled Bulk Drug - CLOXACILLIN (Including its salts, esters, sterio isomers and derivatives);2012 [cited 2013 Apr 8];[about 10 screens] Available from: http://www.nppaindia.nic.in/ceiling/sch-bd-cplist/sch-bd-cloxa.html
58. Department-related Standing Committee on Health and Family Welfare. Fifty-ninth report on the functioning of the Central Drugs Standard Control Organisation (CDSCO) [Internet].New Delhi: Rajya Sabha Secretariat, Parliament of India; 2012 May 8[cited 2012 Sep 21]. 118p. Available from: http://164.100.47.5/newcommittee/ reports/englishcomittees/committee%20on%20health%20and%20family%20welfare/59.pdf
59. Sreedhar D, Subramanian G, Udupa N. Combination drugs: Are they rational? *Current Science*. 2006 Aug 25;91 (4):406.
60. Alexander J. Public interest groups to move court seeking to weed out 294 irrational combos. *Pharmabiz .com*[Internet]. 2007 Dec 27[cited 2013 mar 23]. Available from: http://saffron.pharmabiz.com/article/detnews.asp?articleid=42269&sectionid=50
61. Drugs Control [Internet]. Jaipur, India;[updated 2013 Apr 7].List of FDCs not approved by DCGI. Central Drugs Standards Control Organisation; 2008[cited 2013 Apr 8]. Available from: www.drugscontrol.org/FDCs.xls
62. Narayanan D. Tamil Nadu Medical Services Corporation: a success story. *Forbes India*. 2010 Jul 27[cited 2913 Mar 23]. Available from: http://forbesindia.com/article/on-assignment/tamil-nadu-medical-services-corporation-a-success-story/15562/1
63. Singh PV, Tatambhotla A, Kalvakuntla RR, Chokshi M. Replicating Tamil Nadu's drug procurement model. *Econ Pol Wkly*. 2012 Sep 29;47 (39):26-9.
64. Roy Chaudhury R, Parameswar R, Gupta U, Sharma S, Tekur U, Bapna J. Quality medicines for the poor: experience of the Delhi programme on rational use of drugs. *Health Policy Plann*. 2005 Mar;20 (2):124-36.
65. Ministry of Health and Family Welfare, Government of India. Report of the working group on drugs and food regulation for formulation of the 12th five year plan[Internet]. New Delhi: MoHFW, GoI; 2012 May 9[cited 2013 Mar 23]. Available from: http://planningcommission.nic.in/aboutus/committee/wrkgrp12/health/WG

THANK YOU, REVIEWERS

All submissions to the journal undergo extensive review by internal reviewers from within the journal's Editorial Board, as well as by external peer reviewers. We would like to thank all our editorial board reviewers, and name the following external experts who have reviewed submissions for IJME in 2012-13.

Abhijit Das, Alok Sarin, Amita Pitre, Alireza Bagheri, Anant Bhan , Ananthakrishnan N, Anoop Thekkuveetil, Anuradha Sovani, Bhavin Jhankaria, Chinmayi Arun, Chinu Srinivasan, Cyrus Vakil, DK Srinivas, David Thambu, Dilip Karnad, Gagandeep Kang, Gairik Sengupta, Gopal Dabhade, Gracy Andrew, , Indira KS, JK Lakshmi, Joe Varghese, Leigh Turner, Lopa Mehta, MS Reddy, Manisha Gupte, Manu Kothari, Mariam Hassan, Monica Sakhrani, Murali Poduval, Nandini Rege, Nilima Kshirsagar, PS Ramaswamy, Peush Sahni, Philip Abraham, Pravesh Jung, Premila Lee, Punita Ezhilarasu, Radha Ramaswamy, Raj Vaidya, Rajan Madhok, Rajan Patil, Rajaram Nityananda, , Rajeev Kumar, Rajib Dasgupta, Rama Jayasundar, Raman Kutty, Ramdas Rao, Ratna Magotra, Ravi Ramakantan, Ravindra RP, Renu Addlakha, SP Kalantri, Samiran Nundy, Saima Iqbal, Salla Sariola, Sandeep Bavdekar, Santosh Karmarkar, Saurabh Bhattacharjee, Sita Naik, Sukanya Rangamani, Sunita Simon Kurpad, Supriyo Choudhury, Thomas Eich, Unnikrishnan P, Upendra Bhojani, Upreet Dhaliwal, Urmila Thatte, Vinay Kulkarni, Vina Vaswani, Vijay Thawani, William Joe, Yatin Dholakia.