

# Fixed Dose Combinations and their Ban Issues of Concern

S. Srinivasan\*

*Debates about health-care policy are central to the understanding of the welfare state. One of the mandates of the state is to ensure the sale of safe medicines as also the need for withdrawing harmful drugs the moment it is known to be harmful. Out of the more than one lakh crore rupee sales in the country, almost 45 per cent are FDCs of which 50 per cent are irrational. That is around ₹ 25,000 crore and a lot of which is outright waste of money of the patient on unnecessary ingredients in these irrational FDCs. These irrational FDCs may, in addition, cost the patient much more by way of serious adverse effects and even death. The large FDC market that includes irrational antibiotic combinations also contribute largely to antimicrobial resistance so that routine antibiotics do not work when they ought to. This article highlights how the government of India was forced, due to the scathing reports submitted by the Standing Committee examining Central Drugs Standard Control Organisation, to take steps to ban irrational FDCs. It also critically evaluates the verdict given by Delhi High Court that quashed the government of India's attempt to ban irrational FDCs.*

**Key words:** *banning FDCs, Central Drugs Standard Control Organisation, Pfizer, Kokate Committee, Drugs and Cosmetics Act*

**D**ebates about health-care policy are central to the understanding of welfare state. Article 47 of the Constitution of India (in Part IV, Directive Principles of State Policy) clearly mentions that it is the duty of the State to raise the level of nutrition and the standard of living and to improve public health:

The State shall regard the raising of the level of nutrition and the standard of living of its people and the improvement of public health as among its primary duties and, in particular, the State shall endeavour to bring about prohibition of the consumption, except for medicinal purposes, of intoxicating drinks and of drugs which are injurious to health.

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\*S.Srinivasan (chinusrinivasan.x@gmail.com) is affiliated with LOCOST, Vadodara and All-India Drug Action Network (AIDAN). Both organisations have filed a Special Leave Petition (SLP) in the Supreme Court arising out of impugned common final order and judgment dated 19.05.2016 and 01.12.2016 passed by Hon'ble High Court of Delhi in W.P. (C) No. 2211/2016. Pfizer Ltd and Anr. v. Union of India & Anr. and 453 other petitions.

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One of the mandates of the State is to ensure the sale of safe medicines and this includes withdrawing harmful drugs the moment it is known to be harmful. The Judge in *Macleods Pharmaceuticals Limited and Anr. v. Union of India*, in his final order in April 2012, observed:

If a drug is likely to be harmful or likely to involve any risk, to human beings, the withdrawal of the same from the market, should happen instantaneously, upon the acquisition of knowledge about such potentially harmful effects. It is no argument in such cases to contend that the drug has already had its harmful effect for ten years and that therefore, the redemption from the same can wait for a few months. (para. 70)

### **What is a drug?**

The Drugs and Cosmetics Act 1940 defines drugs as:

All medicines for internal or external use of human beings or animals and all substances intended to be used for or in *the diagnosis, treatment, mitigation or prevention of any disease or disorder* in human beings or animals, including preparations applied on human body for the purpose of repelling insects like mosquitoes. (emphasis ours)(Chapter 1, 3(b)(i))

Consequently, a medicine that does not help in diagnosis, or treat, mitigate or prevent disease or disorder in human beings/animals cannot be called a drug. It is in this context that the attempts made by the government of India to weed out fixed dose combination (FDC) drugs have to be examined.

### **Contextualising fixed dose combination drugs**

FDCs are combination of two or more medicines. FDCs are justified when they demonstrate clearly any of the following benefits in terms of:

- increased therapeutic efficacy;
- reducing the incidence of adverse effect of drugs;
- having pharmacokinetic advantage;
- better compliance by reducing the pill burden;
- reducing dose of individual drugs;
- decreasing development of resistance, and
- cheaper than individual drug because of reduced cost from packaging to distribution. It is important that the above claims are adequately supported by scientific evidence.

Unscientific FDCs leads to unnecessary consumption of medicines exposing the patient to avoidable expenses and unnecessary risks of side-effects, adverse drug reactions and adverse drug-drug interactions. Undesirable, irrational FDCs are those which have:

- Pharmacodynamic mismatch between the two components, one drug having additive/antagonistic effect leading to reduced efficacy or enhanced toxicity;
- pharmacokinetic mismatch and having peak efficacy at different time;
- chemical incompatibility leading to decreased shelf life;
- drug interactions because of the common metabolising pathways; and
- limitations of finer dosing titration of individual ingredients.

FDCs also present difficulties in ensuring quality control (as they are not mentioned in standard pharmacopeias), in rational price fixation, and almost always have to be sold as branded medicines. It is in view of this that the World health Organization recommended that:

Most essential drugs should be formulated as single compounds. Fixed-ratio combination products are acceptable only when the dosage of each ingredient meets the requirements of a defined population group and when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety or compliance. (WHO, 2000, p.5)

### **FDCs in India**

Out of the more than one lakh crore rupees sales in the country, almost 45 per cent are FDCs of which 50 per cent are irrational. That is around ₹ 25,000 crore and a lot of which is outright waste of money of the patient because of unnecessary ingredients in these irrational FDCs.† These irrational FDCs may in addition cost the patient much more by way of serious adverse effects and even death. The large FDC market with irrational antibiotic combinations also contribute largely to antimicrobial resistance so that routine antibiotics do not work when they ought to. In the following section we will examine why FDCs need to be weeded out with suitable examples.

### **Why many FDCs need to be weeded out?**

As Bhargava (2009) mentions the potential risks of unscientific and unnecessary combinations are:

- a) artificial scarcity of effective single ingredient products;
- b) suboptimal therapy;
- c) unnecessary polypharmacy and higher risk of adverse effects;
- d) increase in the risk of drug resistance;
- e) individualisation of drug dosage might become impossible; and
- f) increase in risk of medication errors (pp.4-7).

Numerous examples of dangerous FDC drugs exist. Topical creams, for example,

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† Estimate by author and Malini Aisola from *PharmaTrac*, January 2016.

which are FDCs containing topical corticosteroids cause havoc with the patient's body. Some of these are 'steroid cocktails', which are fixed dose combinations of topical corticosteroids and one or two antibiotics and antifungals. These topical corticosteroid cocktails are irrationally used to:

- a) treat bacterial or fungal infections in combination with antibiotics and/or antifungals;
- b) lighten the skin color in an effort to become fairer; and
- c) suppress any itchy, unsightly or painful rash on the skin regardless of its underlying cause.

Adverse effects of topical steroid FDCs range from topical steroid groin and topical steroid face to adrenal insufficiency leading to death. The annual dermatological market as of July 2017 is ₹ 6896 crore (AIOCD-AWACS, 2017) out of which 85 per cent are FDCs and of which a majority contain topical steroids.

Roy, Malhotra, Tayal, Bansal, and Gupta (2011) in their study of cold and cough FDC preparations in the Indian market found that:

most of the preparations were irrational and had no documented benefit in the treatment of common cold. Availability of such a large number of irrational FDCs for cough and cold requires serious review of the legal provisions in India for drug manufacturing and marketing. (p. 258)

Further, as can be seen in Table 1 over 80 per cent of paracetamol containing medicines are FDCs. Additionally, the FDC preparations circumvent the drug price control as well.

**Table 1: Market for Single Ingredient versus Pombinations of Paracetamol**

	Sales for 12 months ending Jan 2015 (In Crore)	As per cent of total paracetamol market of ₹ 3285.5 cr
Single ingredient formulations in price control	181.6	5.5
Single ingredient formulations not in price control	427.5	13
Fixed Dose Combinations (not in price control)	2676.4	81.5

Source: Analysis by author and colleagues at AIDAN from *PharmaTrac* Data, January 2015

### Legal basis and attempts to ban FDCs

Drugs and their FDCs have been banned ever since Section 26A of the Drugs and Cosmetics Act, 1940 was introduced wef 1-2-1983. It says:

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. (Government of India. Ministry of Health and Family Welfare, n.d., p.20)

Government can initiate action on any drug, including an FDC, to regulate, restrict or prohibit a drug only if it has unacceptable safety ('likely to involve any risk'), or does not have efficacy ('does not have the therapeutic value claimed') or does not have the right ingredients in the right quantities (neither overdose nor sub therapeutic dose) 'for which there is no therapeutic justification'. Further, it must be in the public interest to do so. The provision to regulate and restrict, is a recent introduction to empower the government to ensure certain drugs, like those in Schedule H1, are available only on prescription by qualified medical graduates and specialists. To 'regulate or restrict' a drug without any therapeutic justification or efficacy does not make sense. The only option is to prohibit, that is ban, such a drug from the market. A drug with unacceptable risk/safety, and with safer available alternatives, also needs to be banned.

### **Recent ban of FDCs**

Using the powers under Section 26 A, government of India banned 344 FDCs in March 2016, and five FDCs in June 2017 (Srinivasan, Shiva, & Aisola, 2016, p. 21). The former, i.e., the 344 FDCs, are unauthorised FDCs licensed for manufacture by the State Licensing Authorities (SLAs) without Central government approval as to their safety and efficacy. The latter five FDCs are those approved by the Central government, presumably considered of acceptable safety and efficacy at the time of approval, but on re-examination found to have unacceptable safety, efficacy, and/or therapeutic justification. Both these sets of action on FDCs have their immediate genesis in the observations of the 59<sup>th</sup> Department Related Parliamentary Standing Committee on Health and Family Welfare (PSCHW) *Report on the Functioning of the Central Drugs Standard Control Organisation (CDSCO)*, laid in both Houses of the Parliament in May 2012 (India. Parliament. PSCHW 2012; India, Parliament. PSCHW, 2013; Srinivasan, 2012).

We examine them in sequence. We have reproduced below at length extracts from the 59<sup>th</sup> PSC Report as a sample of the regulatory and therapeutic anarchy that has characterised India's drug administration, if proof was needed.

### **Ban of five FDCs in June 2016**

In order to scrutinise new drug approvals, the 59<sup>th</sup> PSCHW asked for examination of files of 42 randomly selected medicines from the list of new drugs uploaded by CDSCO on its website. The Ministry could not trace files pertaining to three drugs namely, pefloxacin, lomefloxacin and sparfloxacin. The Committee observed that all the drugs:

had been approved on different dates and different years creating doubt if disappearance was accidental. Strangely, all these cases also happened to be controversial drugs; one was never marketed in US, Canada, Britain, Australia and other countries with well

developed regulatory systems while the other two were discontinued later on. In India, all the three drugs are currently being sold....

**The Committee is of the view that due to untraceable files on three drugs, it is not possible to determine if all conditions of approval (indications, dosage, safety precautions) are being followed or not. Moreover the product monographs cannot be updated in the light of recent developments and regulatory changes overseas. Therefore all the missing files should be re-constructed, reviewed and monographs updated at the earliest. (emphasis as in original) (PSCHW, paras. 7.12 and 7.13, p.13)**

The Committee scrutinised the files on offer of the rest of the 39 drugs, among which many were FDCs. The Committee found the following shortcomings with reference to the FDCs:

- Not only Phase III clinical trials mandated by Rules were not conducted in the case of FDC of pregabalin, methylcobalamine, alpha lipoic acid, pyridoxine and folic acid (Theon) but even the opinion of experts was not sought. “The decision to approve these drugs was taken solely by the non-medical staff of CDSCO on their own” (India, Parliament. PSCHW, 2012, para. 7.14, p.14).
- The following FDCs, among others, did not have permission for sale in any of the major developed countries (United States, Canada, Britain, European Union nations and Australia).
  - a) Nimesulide with Levocetirizine (Panacea)
  - b) Etodolac with Paracetamol (FDC)
  - c) Ofloxacin with Ornidazole (Venus)
  - d) Gemifloxacin with Ambroxol (Hetero)
  - e) Glucosamine with Ibuprofen (Centaur)
  - f) Diclofenac with Serratiopeptidase (Emcure)
  - g) Aceclofenac with Thiocolchicoside (Ravenbhel)
  - h) Aceclofenac with Drotaverine (Themis)
  - i) Pregabalin with other agents (Theon)
  - j) Tolperisone with Paracetamol (Themis).

The Committee noted that “None of these drugs have any special or specific relevance to the medical needs of India. (India, Parliament. Rajya Sabha. PSCHFW, 2012, para. 7.14, p.14)

Out of these FDCs (a) to (e) were referred to subject expert committees/New Drug Advisory Committee and they were declared not worthy of continued marketing. The related ban orders came only in June 2017 although the ban recommendations on

three of the five FDCs from the expert committees were in place in 2014. FDC (f), of diclofenac with serratiopeptidase (Emcure), was also not approved for continued marketing but ban orders have not yet been issued. FDC (g), FDC of aceclofenac with thiocolchicoside (Ravenbhel), was declared rational as per an expert committee decision of Jan 15, 2016. The fate of FDCs (h) to (j) is not known.

Regarding FDC (h) in the list above, namely, of aceclofenac with drotaverine (Themis), the Committee Report had this to say:

If the above cases are not enough to prove the apparent nexus that exists between drug manufacturers and many experts whose opinion matters so much in the decision making process at the CDSCO, nothing can be more outrageous than clinical trial approval given to the Fixed Dose Combination of aceclofenac with drotaverine which is not permitted in any developed country of North America, Europe or Australasia. In this case, vide his letter number 12-298/06-DC dated 12-2-2007, an official of CDSCO advised the manufacturer, Themis Medicare Ltd. not only to select experts but get their opinions and deliver them to the office of DCGI (Drug Controller General of India)! No wonder that many experts gave letters of recommendation in identical language apparently drafted by the interested drug manufacturer...

In the above case, the Ministry should direct DCGI to conduct an enquiry and take appropriate action against the official(s) who gave authority to the interested party to select and obtain expert opinion and finally approved the drug....

Such expert opinions in identical language and/or submitted on the same day raise one question: Are the experts really selected by the staff of CDSCO as mentioned in written submission by the Ministry? If so how can they, situated thousands of miles away from each other, draft identically worded letters of recommendation? Is it not reasonable to conclude the names of experts to be consulted are actually suggested by the relevant drug manufacturers? (India, Parliament. Rajya Sabha. PSCHF, 2012, paras. 7.32-7.34, p.19)

### ***FDC of flupenthixol and melitracen (Deanxit)***

Regarding FDC of flupenthixol and melitracen (Deanxit), the 59th PSCHF Report observed:

Except for giving file number (12-62/95-DC) and the date of approval (28-10-1998), the Ministry failed to provide any documents and information on the regulatory process that led to its approval (such as import permission, mandatory clinical trials etc.). The combination contains two drugs, flupenthixol and melitracen. Melitracen has never been approved and used in India. Therefore under Schedule Y, Appendix VI (a), the combination is a “New Drug” for two reasons (i) because one of the two ingredients has not been approved in the past and (ii) because all combinations (FDCs) are classified as New Drugs. CDSCO violated the rules by approving the drug on following counts:

- Drugs and Cosmetics Rule 30-B bans the import and marketing of any drug the use of which is prohibited in the country of origin. Deanxit was and continues to be prohibited for sale and use in Denmark, its country of origin. Therefore permission to import and market was given unlawfully.
- Since Melitracen was not individually approved earlier, the Combination had to undergo all phases of development (Phase I, II and III). Permission to conduct the last phase III, if given was in violation of rules.
- Before approving the indications of a New Drug, it is mandatory to conduct clinical trials individually for all the different indications. A perusal of the Marketing Approval dated 28th October 1998 shows that the approved indications were: (i) Psychogenic depression, (ii) Depressive neuroses, (iii) Masked depression and (iv) Psychosomatic affections accompanied by anxiety and apathy. In its submission the Ministry failed to give details of trials at 3-4 sites with at least 100 patients for each indication as required by law. As per the package insert on Deanxit, the brand is being indicated and promoted for two unapproved indications i.e. “Menopausal depression”, “Dysphoria and depression in alcoholics and drug addicts.” The approval letter issued to the sponsor clearly states at serial number 7: *“No claims except those mentioned above shall be made for this drug without the prior approval of this Directorate (DCGI).”* (italics as in original)(India, Parliament. Rajya Sabha. PSCHW, 2012, para. 7.44, pp. 21-22)

The Committee also contended that there must be some very good reasons why Danish Medicine Agency (Denmark) did not approve a domestically developed drug. Curiously, Deanxit is produced and exported but not sold in Denmark. In view of this the Committee opined that the DCGI should have gone into the reasons for not marketing the drug in major developed countries such as United States, Britain, Ireland, Canada, Japan, Australia just to mention a few. United States alone accounts for half of the global drug market. The Committee opined that the approval of this drug is in clear violation of the Drugs and Cosmetics Rules. As per Rules, a New Drug is deemed to be a New Drug for four years. After four years, the State Drug Authorities have the powers to issue manufacturing licenses without reference to DCGI. Therefore, if initial approval is given unlawfully by the DCGI, the doors open for other manufacturers to market the drug after four years. This is exactly the situation with FDC of flupenthixole and melitracen. The Committee recommended that in view of the unlawful approval granted to Deanxit, the matter should be re-visited and re-examined keeping in mind the regulatory status in well developed countries like Denmark, the country of origin; the United States, Britain, Canada, European Union and Japan etc. (India, Parliament. Rajya Sabha. PSCHFW, 2012, para. 7.47, p.22)

The FDC of flupenthixole and melitracen was finally banned in 2014, after some legal hiccup in 2013. This action was taken only after some strong strictures from the PSCHFW during the 66th Action Taken Report (ATR) on the 59th PSCHW Report meetings.

### **Ban of 344 FDCs in March 2016**

To recap, the FDCs (a) to (j) mentioned earlier were initially approved by the Central

government on the basis of which SLAs issued manufacturing licences, and then subsequently were found by the 59<sup>th</sup> PSCHW Report to be of dubious or unacceptable safety/efficacy/therapeutic justification. On the other hand, the 344 FDCs were essentially unauthorised FDCs as they did not have the requisite Central government approval: one of the reasons the Indian pharma market is awash with FDCs, many of them irrational, that is they would not stand the scrutiny of medical experts. (McGettigan, Roderick, Mahajan, Kadam, & Pollock, 2015).

If they did not have the requisite Central government approval, then how did these FDCs get into the market? The manufacturers of these 344 FDCs directly applied to the SLAs for manufacturing licences. The SLAs granted manufacturing licences for these irrational FDCs without verifying whether they had DCGI approval after due submission of safety and efficacy data. Most of these FDCs were ‘new drugs’ as per Rule 122E of the Drugs and Cosmetics Act which therefore required approval by the Central government before being awarded manufacturing licences by the SLAs. Over the years - especially since 2000 – the DCGI vacillated with the idea of regulating these FDCs and weeding them out if found irrational. A major such effort in 2008 identified about 294 FDCs (running into several brands of different companies) but the effort was stayed by the Madras High Court. The interregnum between 2008-2012 saw several sporadic efforts by the DCGI to regulate these FDCs.

The 59<sup>th</sup> PSCHW identified the presence of these irrational and unauthorized FDCs in the market as a major problem:

To remove such unauthorized FDCs from the market, the Central Government can either issue directions under Section 33P (of the Drugs and Cosmetics Act) to states to withdraw the licences of FDCs granted without prior DCGI approval or the Central Government can itself ban such FDCs under Section 26A.

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It is also possible to ban FDCs, not authorized by CDSCO by invoking Section 26A which empowers the Central Government to ban any drug to protect public health. The Committee was informed that the Government has not evoked Section 26A either so far. No explanation was offered for not using powers under Section 26A.

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The Committee is of the view that those unauthorized FDCs that pose risk to patients and communities such as a combination of two antibacterials need to be withdrawn immediately due to danger of developing resistance that affects the entire population.

The Committee is of the view that ...(t)here 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. (India, Parliament. Rajya Sabha. PSCHFW, 2012, paras. 9.3 – 9.8, pp. 26-27)

In the 66<sup>th</sup> Action Taken Report (ATR) on the earlier 59<sup>th</sup> PSCHW Report, the Parliamentary Standing Committee on Health and Family took the Ministry and CDSCO severely to task for lack of any significant movement on the above observations of the 59<sup>th</sup> PSCHW Report regarding the FDCs without approval. The Committee noted:

**Even after the passage of several months these drugs continue to be marketed with impunity though their exact effect, harmful or otherwise, is yet to be ascertained. The Government without caring a bit about the ramifications is still contemplating referring the issues related to continued marketing of these drugs and updating of their product monographs in the light of recent knowledge and regulatory changes overseas to NDAC for examination and review. The continued inaction of the Government on this vital matter of public health needs to be deprecated in strongest terms. The Committee also recommends that the Ministry should come out of its contemplation mode and take action as recommended by the Committee in the context of these three drugs without any further loss of time. (emphasis as in original)(India, Parliament. Rajya Sabha. PSCHFW, 2013, para. 3.31, p.nd)**

The ATR also observed:

**With piles of evidence available locally as well as in the form of global best practices, the Ministry can do the needful *suo motu* and without resorting to this time tested, time consuming device of an expert Committee. The Committee expects the Ministry to take decisions in the matter accordingly at the soonest so that the approval of FDCs is regulated by well laid out policies, guidelines and procedures expeditiously. (emphasis as in original)** (India, Parliament. Rajya Sabha. PSCHFW, 2013, para. 3.149, nd)

It is such pressure from the 59<sup>th</sup> PSCHW that resulted in the government finally acting. The DCGI, in January 2013 asked manufacturers who had not got approval from the Central Government to produce safety and efficacy data of their FDC products, or face the risk of cancellation of their licences. This direction was applicable to all products approved after Sep 29, 1988 and before October 1, 2012. Most manufacturers complied after the usual attempts to stall the process by lobbying, etc. The deadline for submission of safety and efficacy data was set for July 14, 2014.

### **Kokate committee recommendations**

To examine the 6,220 applications, the government initially appointed subject expert committees and then to speed-up up the process appointed a committee of experts

chaired by Professor C. K. Kokate (hence know as Kokate Committee). The Committee was tasked with the responsibility of identifying the FDCs in the market that were grossly irrational/unsafe based on pharmacokinetic and pharmacodynamic interaction, dosage compatibilities of FDCs vis-a-vis that of single ingredients.

The Kokate Committee examined the 6,220 applications received and finally identified 963 irrational FDCs representing 344 FDCs. After due deliberations, show cause notices to manufacturers as to why their licences cannot be cancelled, etc., were issued. Subsequently, after several reminders and deadline extensions for response to the show cause notices, and further examination of the responses received, the Committee made its recommendations to ask the government to issue ban orders on 344 FDCs. Despite this the affected companies would, at a later date, complain of no due notice, lack of due process, etc., which was anything but true.

The ban orders were issued in March 2016 under Section 26 A, as a first list of unsafe, ineffective and irrational FDCs. The Kokate Committee also identified another 1629 applications for further deliberation with expert committees, deemed 2617 applications as rational FDCs, and categorized 309 applications as FDCs needing further generation of data.‡

### **Delhi High Court stay order**

The Delhi High Court stayed the ban order - dated 14.03.2016 in W.P.(C) 2212/2016 & CM No.9517/2016; and finally in its order of December 1, 2016 quashed the ban orders on the 344 FDCs on the single reason of not consulting the statutory body Drugs Technical Advisory Board (DTAB) (*Pfizer Limited & Anr. v. Union Of India & Anr.*, 2016). This action of the Hon'ble High Court of Delhi at New Delhi completely overlooked the caution given by the Supreme Court in *Union of India & Ors. v. M/s Cipla Ltd. & Anr.*, (2016) and *Union of India v. Cynamide India Pvt. Ltd.*, (1987). In the latter case, the Supreme Court observed specifically in context of drug prices that the interest of the consumer public that must come first and any interim order must take care of that interest. The Madras High Court about the same time refused to stay the ban of the 344 FDCs by order dated 22.03.2016 in W.P. Nos. 10536 to 10538 of 2016.

The matter has gone on appeal to the Supreme Court by way of a Special Leave Petition (SLP) both by the government of India and All-India Drug Action Network (AIDAN) and Others and the matter is expected to come up for final hearing in late September 2017. Incidentally, the Delhi High Court, during March-June 2016, after hearing the counsel for AIDAN and Others decided, without providing any proper reasoning, not to implead AIDAN. The government also requested that all petitions filed by various companies in various State High Courts in the 344 FDC ban case and recently in the 5 FDC ban case, be transferred to the Supreme Court. The Supreme Court accepted the same.

### **Issues of law**

Several issues of law were raised during the arguments in the Delhi High Court hearings

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‡ These figures were submitted to the Delhi High Court by the government counsel during the arguments on vacating the stay of the ban orders during March-June 2016.

following the stay given by the Court. As they are likely to be repeated in the Supreme Court by the parties concerned, we mention some for their intrinsic interest.

### **Manner of grant of stay**

In discussing the ban order, the Delhi High Court considered only the Pfizer petition related to ban of Corex – as it felt the nature of challenge was similar in all the other 453 petitions challenging the ban orders.

Pfizer was arguing against the ban on its product Corex syrup (an FDC of Chlorpheniramine Maleate + Codeine Syrup). Some of the arguments advanced by the Pfizer as to why stay need to be granted, included: i) Corex is being marketed by Pfizer for the last 25 years; ii) that no enquiry was made from Pfizer or show cause notice issued prior to the ban order and, iii) that the said drug in the same combination is being marketed in other countries. Point (ii) was erroneous in fact. What was surprising however was that Hon'ble Delhi High Court used some of the same arguments in granting the stay considering that the drug so banned has been marketed by the petitioner for the last 25 years and further considering the fact that the:

“impugned Notification, save for generally stating that the use of the said drug was likely to involve risk to human beings did not disclose any grave urgency, the effect of the Notification was stayed and the respondents restrained from taking any coercive steps against the petitioners or its stockists / agents pursuant to the said Notification. (*Pfizer Limited & Anr. v. Union Of India & Anr.*, 2016, para 2, p.4)

The fact that a drug was in the market for 25 years or even 50 years cannot be an argument for its safety and efficacy, especially when a committee of experts, the Kokate Committee, thought otherwise. Likewise, all the other 453 products were likely to ‘involve risk to human beings’ but in the Court’s wisdom risk to human beings does not constitute grave emergency. The Learned Judge of the Hon’ble Delhi High Court could have invoked the precautionary principle and let the orders be instead of staying them and eventually quashing the ban orders.

The Hon’ble Madras High Court, when refusing to stay the ban of 344 FDCs, opined in its order (in W.P. No. 10536 and W.P. No. 10538 of 2016 by order dated 22.03.2016):

We are of the view that the mere fact of the sale of medicines for the last so many years ipso facto cannot call for the sale to continue when an expert body has gone into this issue. We are not dealing with a perishable commodity. There is a shelf life. Further, the larger public interest would weigh in favour of not staying the effect of the notification. We, however, are inclined to give limited protection to the extent that if no sales are made as per the notification, in the meantime, coercive steps be not initiated against the manufacturers, stockists/agents, in view of the stock which would have already been manufactured .

### **Pfizer’s no objection certificate (‘NOC’)**

Even as Pfizer through its counsel was asserting during the March-June 2016 hearings in the Delhi High Court, that Corex was safe, extant literature in the USA warned of

‘death related to ultra rapid metabolism of codeine to morphine’ and other dangerous adverse reactions (Tobias, Green, Coté, AAP Section on Anesthesiology and Pain Medicine, & AAP Committee on Drugs, 2016). In April 2015, the European Medicines Agency (EMA) had announced that codeine must not be used to treat cough and cold in children under 12 years, and that codeine is not recommended in children and adolescents between 12 and 18 years who have breathing problems, including those with asthma and other chronic breathing problems. The Hon’ble Delhi High Court could have been cognizant of the human implications of giving a stay on Corex even as the balance of interest lay with the public.

Indeed Pfizer claimed its approval was legitimate by relying on a NOC purportedly given in 1995 given by the then DCGI. It did not produce any safety and efficacy data in support of its product. The government itself submitted that it had no copy of the NOC in its records. Indeed there is no provision for such an NOC in the law. And the legal route to getting an approval from the Centre rests on submitting data in Form 44 showing safety, efficacy and therapeutic justification. Pfizer did not submit any such data despite knowing that the DCGI had given sufficient notice through various channels including industry associations and had requested submission of such data in case the product had no approval from the Centre. Pfizer, and a couple of other companies, chose to ignore the DCGI’s appeal and preferred to rely on an illegal and invalid NOC so-called. In fact in a peculiar twist of logic, Pfizer argued the burden was on the government to show that the drug was unsafe and it was not for Pfizer to demonstrate efficacy, safety and therapeutic justification!

Unfortunately, instead of investigating as to how such an NOC was granted without safety and efficacy data being on record, the government made a ridiculous and unwarranted concession in the Court to the effect that it proposed to argue on the basis that even if the drug companies had approvals from DCGI the impugned orders were still valid. Probably it was a tactic to get out of the embarrassment of the illegal NOC issue, and also probably the lack of confidence in the government’s own list of drugs approved (put up by it on its website in 2013). The concession nevertheless deprived the government of a vital argument for the ban. Indeed the Court’s position was that the validity of the approvals was not a basis on which the 344 ban orders were formulated. It even raised the issue whether validity or otherwise of the approval can be a basis for ban of a drug under Section 26 A. This reading of the order is erroneous as the causal chain of events tells a different story. Lack of authorised approvals led to the government’s request for submission of safety and efficacy data that lead to Kokate Committee’s examination of the data that eventually led to the ban. The ban order cites lack of therapeutic justification and likely risk to human beings – a conclusion arrived at by the Kokate Committee. The terms of reference of the Kokate Committee were wide enough to cover the eventual sequence of events and their denouement.

### **Migration and *forum conveniens***

The Hon’ble Delhi High Court also probably erred in allowing it to be used by manufacturers – through 454 petitions in all - who migrated from all over the country to Delhi High Court when they realized it was easy to get stay orders on the FDC

bans. The Hon'ble High Court could have invoked the doctrine of forum conveniens (convenient forum or venue) and refused to give the stay orders. But the Court on the contrary issued stays to all without opening each of the petitions dealing with FDCs that was vastly different in efficacy and safety claimed. The other matter of concern is that the Court did not involve any of the SLAs who were actually guilty of wrongfully issuing manufacturing licences. This raises the question whether the judgment of the Hon'ble Delhi High Court quashing the ban orders is maintainable.

### **Consultation with DTAB**

As mentioned earlier, the central argument of the Hon'ble Delhi High Court in its final order of Dec 1, 2016, quashing the ban on the 344 FDCs was based on its interpretation of Section 26A of the Drugs and Cosmetics Act that the DTAB needs to be consulted before banning the drugs. As this did not happen in the current case, the ban orders were considered infructuous.

However it must be noted that Section 26A says that the government has to be satisfied of the lack of safety, efficacy and therapeutic justification of a drug to ban a drug. How government obtains the satisfaction, as long as it has relied on expertise of acknowledged experts selected on objective considerations, is immaterial. Therefore to ignore the Kokate Committee recommendations, is not in the interests of the public at large; indeed we argue that it has caused untold harm nationwide by letting unapproved FDCs continue to be marketed.

Moreover, banning a drug under Section 26A is akin to a legislative act and not an administrative or non-legislative act. Any act of general application is a legislative act and therefore there is no need to provide a hearing to those affected which was not the case anyway in the instant case. More importantly, judicial review of a legislative act like exercise of powers under Section 26A, the Courts cannot really question how satisfaction was reached by the relevant authority (*Union of India v. Cynamide India Pvt. Ltd.*, 1987).

The comment in 59<sup>th</sup> PSCHW Report is very pertinent in this context :

The reply merely states that such dubious drugs are examined in “*consultations with the experts/DTAB.*” The response raises many questions:

- Firstly, at the time of approval of drugs, the matter is not referred to DTAB, then why should DTAB be involved when drugs are to be banned? Secondly, many drugs have been approved by DCGI without consultations with experts; why involve them when banning? There is no answer to these specific questions. It must be made clear that the Committee is not suggesting that DTAB should not be consulted. On the contrary, extensive consultations should take place not only while banning but also approving the drugs. There should be no double standards.
- There is no standard, uniform, transparent system of referral for expert opinion before a drug is banned. In some cases the opinion of DTAB is obtained such as rimonabant, sibutramine and rosiglitazone; in others it is

not obtained but is referred to an Expert Committee appointed by CDSCO such as levonorgesterol, letrozole, nimesulide. In yet other cases such as rofecoxib and valdecoxib, the matter was neither referred to DTAB nor to CDSCO-appointed expert committee.

In most cases, most of these experts whether appointed by CDSCO or DTAB are from Delhi.... One wonders whether expertise on drugs is confined to Delhi. (India, Parliament. Rajya Sabha. Department – Related PSCHFW, 2012, paras. 8.9 and 8.10, pp.25-26)

The 59<sup>th</sup> PSCHFW Report also inter alia recommends that Section 26-A of the Act is adequate to deal with the problem of irrational FDCs. It suggests standard, uniform, transparent system of referral for expert opinion before a drug is banned but does not suggest that such expert opinion has to be necessarily validated through the DTAB. As the above examples show, bans have taken place with and without the consultation or mediation of the DTAB. The DTAB incidentally cannot be considered an objective body as it has pharma industry representation.

The argument that consultation with the DTAB is mandatory before exercise of Section 26 A, does not hold water in the considered view of the Madurai bench of the Hon'ble Madras High Court in *Macleods Pharmaceutical v. Union of India*, (2012):

Therefore, it is clear that any ban order imposed by the Central Government has to be tested only on the strength of the parameters laid down in Section 26-A itself and not with reference to any extraneous material, as the scope of judicial review in such matters is extremely circumscribed. Rather than throwing public interest to the winds and exposing the community at large to the risks associated with drugs that are potentially harmful, the Court could even choose to err on the wrong side....

While the advisory role of DTAB is indicated in broad and general terms in Section 5(1), it is indicated in specific terms in Sections 6(2), 7(1), 8(2), second proviso to Section 10, 12(1) and 33(1). Therefore, the absence of any reference to such requirement of consultation in Section 26-A assumes great significance. It is a well settled principle of interpretation of statutes that the Courts are not expected to supply the omission. The Parliament had consciously incorporated the expressions “after consultation with the Board” or “on the recommendation of the Board”, in certain provisions of the Act such as Sections 5(1), 6(2), 7(1), 8(2), second proviso to Section 10, 12(1) and 33(1). But it has deliberately omitted to include any of those expressions while inserting Sections 26-A and 26-B. It is a case of *casus omisus* [sic]. Therefore, the argument that the Central Government ought to have taken the consultation of the DTAB before issuing the ban order, can hold good only if I can supply into Section 26-A, what was deliberately left out by the Parliament. This cannot be done by me and hence the first contention has to be rejected. (paras. 33 and 39)

Indeed, if the DTAB is not involved in the approval of a drug, there is no reason why it ought to be involved in a ban on the drug. There is no mandate to the government

in the Drugs and Cosmetics Act to consult the DTAB for exercise of powers under Section 26 A.

However, if one peruses the judgment of Dec 1, 2016 quashing the ban orders, the learned judge of the Hon'ble Delhi High Court while correctly observing that the technical content of the ban orders was outside the scope of judicial review, seemsto be supplying the missing phrases in Section 26A when he opines that DTAB has to be consulted for exercise of the powers under Section 26A to prohibit, regulate or restrict. According to him:

a mere absence of the said words (i.e., consultation with the DTAB) from Section 26 A would not mean Section 26 A can be read in isolation ... it will be the domain of the DTAB to advise the Central Government in exercise of all technical powers under the (Drugs and Cosmetics) Act, whether the relevant section prescribes for the Central Government to before exercising of power thereunder take advice of Central Govt or not. (*Pfizer Limited & Anr. v. Union Of India & Anr.*, 2016, para 42)

And in para 50 of the same judgment of the Hon'ble Delhi High Court:

The whole purpose of constitution of DTAB, DCC and setting up of Central Drugs Laboratory would be lost if it were to be held that the Central Government, even in exercise of technical powers under Section 26A or in carrying out other functions assigned to it under the Act is not required to consult them and is free to choose the person from whom it may at that point of time take consultation. No such power has been vested under the Drugs Act with the Central Government. (*Pfizer Limited & Anr. v. Union Of India & Anr.*, 2016)

The Learned Judge in *Macleods Pharmaceuticals Limited and Anr. v. Union of India*, (2012) on the other hand, observed that if it was the intention of the law makers to mention the role of the DTAB in exercise of powers in Section 26A to regulate, restrict or prohibit a drug, they would have done so by including in Section 26A, the phrase "after consultation with or on the recommendation of the Board", despite including such a phrase in various other sections – namely, Sections 5(1), 6(2), 7(1), 8(2), the second proviso to Section 10, 12(1) and 33(1) of the Drugs and Cosmetics Act. The judge also noted:

The maxim 'judicis est jus dicere, non dare' pithily expounds the duty of the court. It is to decide what the law is and apply it; not to make it." Judges are not expected to and supply phrases in law "by engrafting on it or introducing in it, under the guise of interpretation, by analogy or implication, something what it thinks to be a general principle of justice and equity. To do so 'would be entrenching upon the preserves of legislature' (at page 65 in *Prem Nath, L. Ganesh Dass Vs. Prem Nath, L. Ram Nath* (AIR 1963 Punjab 62) per Tek Chand, J.), the primary function of a court of law being jus dicere and not just dare. (*Macleods Pharmaceuticals Limited and Anr. v. Union of India*, 2012)

On the plea by the petitioner that the drug that was banned was in the market for at least 10 years and hence there was no urgency for the government to ban, the Learned Judge in Macleods comments:

At the outset, it has to be pointed out that in matters concerning public health, the court cannot allow time to run, on the specious plea that we have already waited or suffered for ten years. If a drug is likely to be harmful or likely to involve any risk, to human beings, the withdrawal of the same from the market, should happen instantaneously, upon the acquisition of knowledge about such potentially harmful effects. It is no argument in such cases to contend that the drug has already had its harmful effect for ten years and that therefore, the redemption from the same can wait for a few months. (*Macleods Pharmaceuticals Limited and Anr . v. Union of India*, 2012)

Indeed if a drug is bad and/or harmful, it cannot be allowed to be in the market even for a single day.

### **What needs to be done**

The Kokate recommendation for ban on the 344 FDCs essentially accounts for only ₹ 2019 crore (AIOCD-AWACS, 2017) – which is less than 2 per cent of the total domestic market whereas as per our estimate cited earlier, the irrational FDC market is around Rs 25,000 crore. Government needs to act in weeding out the rest of the irrational FDCs too.

Unscientific irrational FDCs are a threat to the right to life and health of the patients. The following steps need be taken by the government –

- a) All irrational FDCs need to be weeded out and enabling legal processes and SOPs need to be clarified.
- b) Broad principles of what constitutes irrational FDCs need to be specified – for example all topical steroid containing topical FDCs must be deemed irrational as well as harmful.
- c) All FDCs which contain one or more of the medicines listed in the National List of Essential Medicines 2015 and all FDCs which contain one or more of the other essential and life-saving medicines marketed in India should be brought under price control.
- d) A central registry of all FDCs and drugs licensed for marketing and/or manufacturing in India would need to be put in the public domain.

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