Public Health Policy Making and Drug Industry
Issues in Knowledge Legitimation

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The political economy of the pharmaceutical industry defines truth significantly, if not substantially and wholly, in medicine as much as does dominant medical practice. This mediated wisdom of medicine is purveyed across populations through public health policies affecting millions as is seen in the following: The fiat of an almost compulsory vaccination schema or a doubtful provider-controlled contraceptive programme. This paper explores the complex realities of the influence of the drug industry on widespread therapeutic practices and health policies and poses some fundamental questions.

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In this essay, we try to survey, admittedly in a very selective way, some endemic features of public health policy making and pharmaceuticals. In passing, we interrogate the beliefs on which some decisions involving medicines and therapeutics are taken, which regrettably, have systemic effects – on populations across the country and on the poorer communities who constitute the majority of Indian citizens.

We first sketch the scenario of the pharma industry which influences many of the decisions taken in health policy making: the ability of India to make/not make certain pharmaceuticals, medicines and vaccines, and to provide affordable access to the consumer. We review a few cases of certain drugs and vaccines, the political and moral economy of the clinical trial process, the papers that get/do not get published, the construction of diseases and the processes that underpin what drugs rule the market, and the sheer irrationality of it all where application of mind is the exception than the rule - in a bizarre twist to the Tagorean phrase, where the mind is without fear, even as the line between valid and invalid knowing, and the demarcation between the clear stream of reason and unreason gets blurred.

I
Pharma Scenario in India

In 2006-07, India's drug prices were among the lowest in the world (dollar terms and even in purchasing power parity terms) with China as the possible exception for even lower prices.

Some Peculiar Features [1] of Pharma Market

India has a vast pharma market, and is rightly celebrated in international circles for making medicines very affordable and low-priced. As of 2003, the Indian industry was

supplying 20 per cent of the world's drugs (by volume) and is currently one of the largest pharma industries in the world (by volume).[2] (See also Box 1)

India as Pharmacy of the World

- **India is the** main supplier **of essential medicines for developing countries.**
- 67 % of medicines produced in India are exported to developing countries.
- **Main procurement agencies for developing countries' health programmes purchase their medicines in India, where there are quality products and low prices.**
- **Approx.** 50% **of the essential medicines that** UNICEF **distributes in developing countries come from India**
- 75-80% **of all medicines distributed by the** International Dispensary Association (IDA) **to developing countries are manufactured in India. (IDA is a medical supplier operating on a not-for-profit basis for distribution of essential medicines to developing countries.)**
- **In** Zimbabwe, 75% **of tenders for medicines for all public sector health facilities come from Indian manufacturers**
- The state procurement agency in Lesotho, NDSO, states it buys nearly 95% of all ARVs from India.
- Antiretroviral medicines (ARVs) for AIDS treatment: India is the world's primary source of affordable ARVs, as it is one of the few countries with the capacity to produce these newer medicines as generics. Therefore, all AIDS programmes use India as their main source of products.

[Source: http://www.accessmed-msf.org/prod/publications.asp?scntid=29120071111256&contenttype=PARA&]

How many drug units are there and how many formulations are made in India? As against the frequently quoted figure of about 20,000 manufacturing units, the actual number of drug manufacturing licenses issued was - bulk drugs (1333), formulations (4534), large volume parenterals, (134) and vaccines (56). The total number of manufacturing units engaged in the production of bulk drugs and formulations is not more than 5877. According to the Director, National Pharmaceutical Pricing Authority of the Government of India (NPPA), the number of APIs (Active Pharmaceutical Ingredients) used is 550, APIs manufactured is 400, formulations marketed are 20,000 under 8000 brand names.[3] The NPPA monitors 20,000 formulations and according to its figures, 56 per cent of these formulations available are based on a single ingredient bulk drug, 20 per cent on two bulk drugs, 8 per cent on three bulk drugs, 4 per cent on four bulk drugs, 2.5 per cent on five bulk drugs and 9.5 per cent on five or more bulk drugs.

Nevertheless there are some peculiar features of this pharma and health services market – true not only for India but all over the 'free market' world too.[4]

- Competition does not work in India's pharma formulations market.[5] The notion of a free market in pharma and health services is a contradiction in terms (see Table 1 below).
- However India's pharma sector is a "free" market in a different sense for a long time: one could make all kinds of irrational drugs from fresh human placenta, animal liver and pig's blood as also arbitrary combinations of different kinds of medicines and sell them at arbitrarily high prices.
- In India, the same drug is sold at vastly different prices by equally reputed companies and often by the same company.[6]
- Brand leader is often the price leader! That is the most popular brand of a drug is also often the highest priced.
- Medicines are the only commodity in which the end-user (the paying patient) does not decide what to buy and at what cost. The doctor prescribes and the patient pays. In addition, in India every doctor decides on his/her own which brand of which medicine to prescribe.
- There is no choice for the consumer in this market. Unlike in case of other commodities the purchaser of medicines is extremely vulnerable as he/she is seeking immediate relief from suffering.
- These asymmetries in information, in the doctor-drug company interface as much as in the doctor-patient and drug company-patient, is what leads to market failure. This special nature of drugs is the reason why even in market economies, all issues related to drugs including their prices are the subject of regulation by their Governments. The only exception is the USA – even in the USA the prices of drugs are indirectly regulated by health maintenance organisations negotiating prices to be paid on prescription costs. (The Government's own committees have reported that even in the so-called free market countries there is price control of some kind or the other.)
- Pharma is the only sector in India (and probably in the world) where government tender procurement prices are 1-3% of the retail market prices! This if anything indicates the level of overpricing.[7] An example: for the Tamil Nadu Government, a drug company bids to supply Albendazole 400 mg tablets, a medicine for worms, at a mere 35 paise per tablet, while brands of this drug sell for Rs.12/- in the market.

- India's pharma markets are full of unnecessary, unscientific and therapeutically useless drugs. This leads to further market distortion and market failure.[8] We need to immediately weed out all these drugs by allowing only drugs as per the WHO essential drug list or the Government's own National List of Essential Medicine (NLEM) 2003.
- If one studies the ORG-Nielsen list of top-selling 300 drugs accounting for more than Rs 25,000 crores sales (almost 90 per cent of the retail market), atleast 60 per cent of the top-selling 300 drugs are not in the NLEM. Therefore 2/3rds of drugs sold in India are not essential drugs by the Government's own definition.

And from the user's point of view:

- A serious indictment of the pharma industry is the lack of public health relevance of many of these top-selling preparations. Take the case of preparations for iron deficiency anemia, which is one of India's most prevalent public health problems. There is not a single preparation in the top 300, which has the ingredients for an anemia preparation as mentioned in the National List of Essential Medicines (NLEM).
- The major crisis in drugs in India is one of availability (in the public systems), access and affordability to the poor and the middle class.
- India has the largest number of people, an estimated 649 million, without access to essential medicines. (*World Medicines Report 2004,* WHO)
- In India, unlike in the developed countries, expenditure on medicines constitutes a large proportion (>50%) of total medical expenditure. About 80-90% of this expenditure is out-of-pocket expenditure by the people since the government spends a very small proportion on medicine procurement.[9]
- Unlike in the developed countries, most Indians patients face the drug industry as hapless individuals because most are not covered by insurance or social security mechanisms.
- Majority of Indians are below or near poverty-line, yet they are forced to spend on unnecessarily costly medicines. This unnecessary expenditure on medicines is a very important cause for indebtedness before and after hospitalization.

Table 1: 'Free' Market of Branded Drugs - What Happens When There Is No Price Regulation

Sl. No.	Name of Drugs	Drug Under price control	Lowest Price of Brand in Rupees/Brand Name/ Manufacturer	Highest Price of Brand in Rupees/Brand Name/ Manufacturer	Highest priced brand/lowest priced brand x 100
Drugs for bacterial infections: like pneumonia, urinary tract infections					
1.	Ofloxacin 200 mg	No	Rs. 3.20/Zo/FDC	Rs 31.00/ Tarivid/Aventis	969%
2.	Levofloxacin 500 mg	No	Rs. 6.82/Levoflox,/Cipla	Rs 95.0/Tavanic/ Aventis	1392%
3.	Ciprofloxacin 500 mg	Yes	Rs. 3.90/ Zoxan/FDC	Rs. 8.90/ Cifran/Ranbaxy	228%
4.	Azithromycin250 mg	No	Rs 8.50/Zathrin, FDC	Rs.39.14/ Vicon/Pfizer	460%
Drugs Used in Viral Infections including HIV/AIDS					
5.	Zidovudine 100 mg	No	Rs. 7.70/Zidovir/Cipla	Rs. 20.40/Retrovir/ GSK	265%
Drugs Used in Heart Disease, Hypertension, High Cholesterol					
6.	Amlodipine 5 mg	No	Rs. 1.51/Amlodac/Zydus Cadila	Rs. 6.00/Amlogard/ Pfizer	397%
7.	Atenolol 50 mg	No	Rs. 0.40/Ziblok,/FDC	Rs. 2.45/Tenormin/ Nicholas Piramal	612%
8.	Valsartan 80 mg	No	Rs. 5.90/Valzaar/Torrent	Rs. 41.00/Diovan/ Novartis	694%
Drugs Used in Diabetes					
9.	Pioglitazone 15 mg	No	Rs. 0.99/Pio/Systopic	Rs 6.00/Piozone/ Nicholas Piramal	606%
10.	Glimepride 1 mg	No	Rs. 0.80/ Glimestar/Discovery/ Mankind	Rs 5.30/Amaryl/ Aventis	696%
Drugs Used in Cancer					
11.	Tamoxifen 10 mg	No	Rs. 2.70/Tamodex/ Biochem	Rs. 20.00/Nolvadex/ ICI	741%
12.	Letrozole 2.5 mg	No	Rs. 9.90/Oncolet/Biochem	Rs. 181.50/ Femara/Novartis	1833%
Drugs for Psychiatric Ailments					
13.	Risperidone 2 mg	No.	Rs.1.69/Respidon/Torrent	Rs. 27.00/Risperdal/ Ethnor	1598%
Drugs for Metabolic Disorders					
14.	Risedronate 35 mg	No	Rs 50.12/Risofos/Cipla	Rs500.00/Actonel/ Aventis	997 %
Drugs for Arthritis					
15.	Leflunomide 10 mg	No	Rs 8.00/Rumalet/Zydus Cadila	Rs 44.00/Arava/Aventis	550%
Drugs for Erectile Dysfunction					
16.	Sildenafil citrate100 mg	No	Rs 29.16/ Penegra/Zydus Alidac	Rs 584.00/ Viagra/Pfizer	2002%

Committees of the Government: Disjunct Between Left and Right Hands

The Report of the Standing Committee on Chemicals & Fertilizers, 2005-06, Fourteenth Lok Sabha observes:[10]

> The Committee's examination revealed that though, there is a provision that a strict watch will be kept on the movement of the prices and the Government may determine the ceiling levels beyond which increase in prices would not be permissible, this provision has seldom been applied. In this context, some of the State Governments have also informed that when the cases of high prices of Anti-cancer drugs, Antibiotics, Nutraceuticals and Cetrizine were referred to the National Pharmaceutical Pricing Authority (NPPA), the latter conveyed its helplessness in curtailing the high prices. The Committee are unhappy over this unsatisfactory state of affairs and desire that the situation should be remedied forthwith. They therefore, recommend that for the category of drugs for the same therapeutic use, the Government should determine a reasonable ceiling beyond which increase in prices may not be allowed.

Several other expert committees set up by the Government of India, in post-liberalization times, have also stressed the importance of drug price regulation.[11] For instance: the Drug Price Control Review Committee of 1999, the Sandhu Committee of 2004, and a Task Force appointed by the PMO in 2005 and chaired by Pronab Sen from the Planning Commission, the Commission on Macroeconomics and Health 2004, etc. However industry does not want controls of any kind and in accordance with the wishes of the pharma industry, the number of drugs in the price control basket has come down over the years from over 347 in 1979 to 74 in 1995 – it would have been less than 30 if the Pharmaceutical Policy 2002 were not stayed by the Supreme Court.[12] The Court directed the Government of India to first decide the basket of essential drugs to be put under price regulation and a methodology thereof. In response the Government came out with the National Essential Medicines List [NEML 2003] in which there are some 354 drugs. The Pronab Sen Committee recommended all these drugs (as well as equivalent drugs in the same therapeutic class) be put under regulation/monitoring/control; and fixed dose combinations of these drugs would have the same price ceiling too – a measure that would have discouraged irrational combinations at one stroke. This was too much to swallow and not to the liking of the industry and therefore severe lobbying has resulted in a series of committees involving the 'industrywallahs' – the latest a Joint Committee consisting of the pharmaceutical industry (12 members) and four members from the Ministry of Chemicals and Fertilizers. This committee is supposed to provide recommendations on price monitoring and control. No representative from the Ministry of Health, let alone patient groups and public interest organizations, has been included in the Committee. In the meanwhile, a packet of oral rehydration salts can cost Rs. 14 (approaching the retail price of a bottle of saline), rural patients with tuberculosis spend

Rs. 1000 per month on therapy, a patient with a dog bite spends Rs. 1545[13] on the cost of vaccines alone and some antibiotics and anticancer drugs are consumed at a cost of Rs 6000 per day.

Behaviour of Stakeholders

The way the pharma market has developed in India, there are serious barriers for ethical and scientific behaviour, thanks to the nexus between industry, government and the medical profession (with few exceptions). For activists and NGOs concerned with access to health issues, having an essential drugs list, weeding out irrational drugs and price control on all essential drugs have been a high priority in their campaign agenda. Whereas for industry, the first two issues are a laugh and believe that competition and market would decide quality and price and the kind of drugs to be made available. They tend to focus of late on R &D and exports even as it gives them legitimacy to wrest more tax concessions from the Government. Industry lobbies for reducing the number of drugs to be put under price control. Government on its part has seldom in the last 10 years paid any interest on issues of essential drugs, irrational drugs and pricing except when goaded by the Supreme Court. In fact the current dominant trend in Government among various concerned ministries is to go all out and make the market free of price controls, with pharma parks on the lines of SEZs thrown in for good measure. This goes along with reluctance to use compulsory licenses (legit under India's own amended patents act of 2005 as well as under TRIPS/WTO).

A current draft policy (circa December 2006) doing the rounds has these as key objectives of the policy:[14]

(a) To ensure availability at reasonable prices of good quality medicines within the country,

(b) To improve accessibility of essential medicines for the common man, particularly the poorer sections of the population,

(c) To facilitate higher investment for increased production of good quality medicines,

(d) To promote greater research and development in the pharmaceuticals sector by providing suitable incentives and encouraging public private partnerships in R&D and improving institutional infrastructure,

(e) To enable domestic pharma companies to become internationally competitive by implementing GMP, GLP, GCP and other established international guidelines,

(f) *To facilitate higher growth in exports of APIs and formulations by reducing the barriers to international trade in pharmaceuticals sector,*

(g) To develop India as the preferred global destination for pharma R&D and manufacturing,

(h) To facilitate implementation of the Health Policy of the country through improved availability of quality medicines in the country. *(emphasis ours)*

Professional medical associations as well as academicians generally skirt the issues of political economy of the pharma industry as also being mostly unaware, by choice or by nature's course untrimmed, of issues related to rationality, essential drug list, hazardous drugs, access to affordable medicines, etc.

What of the end user? Consumers being mostly illiterate, and uninformed – even if educated otherwise – take what is on offer reposing their faith in the prescriber, the retail pharmacist or even the grapevine. Consumers have little or no choice in the matter – except the choice not to consume medicines even if under distress. Standard economics has a way of explaining this by saying since there is an extreme asymmetry (famously analysed by Akerlof[15] in his "The Market for 'Lemons.'"). In the instant case, the consumer may not get lemons most of the time, but tends to do so for a significant part of the time, and in the absence of regulation of the drug industry and of medical practice, lemons are what a poor person gets on the whole. Lemons in the skin of alphonso mangoes. Indeed as one rural doctor friend of the author points out:

> In no other situation in life does a consumer buy goods of which he/she has no knowledge, buys on the written recommendation of a second party from a third party; and the second party may charge heavily for doing so; and the second party may also get paid by third party and other parties manufacturing those goods; and bought usually at a time of severe distress with death as a possible threat of non-purchase. Is this not, combined with the above irrationalities, sufficient cause for thorough overhaul of the drug control and pricing system of India?

There is a difference though with Akerlof who tried to show for instance that "the market for used cars--because of asymmetric information--is likely to be quite a small market and that other markets with sufficient asymmetric information will, in fact, collapse and will not be there at all. The leading and most obvious such failure is in health care

insurance." In the case of the pharma sector in India, the market exists, it is anything but small, may be even flourishing, but as a paradigm of meeting health care requirements efficiently in the long run, it appears to be a failure. This prevalence of chaos is seen as an argument for health insurance, not necessarily State-guaranteed universal health insurance, with every danger that health insurance premia would be priced out of the reach of the poor.

There is a serious need for the pharma industry to change to accommodate to reality. "An economist's definition of hatred," according to behavioural economist Edward Glaeser, "is the willingness to pay a price to inflict harm on others."[16] The homo economicus types in the drug industry, pharma trade, in the regulatory agencies and in the government have decided that they are willing to pay the short-term and long-term price for inflicting misery on the poor of India. Assured in their calm belief they can get away with it. Methodologically and temporally.

II
Knowledge Legitimation Practices in Routine Medical Practice: Legitimising Illogic and Unreason

Prevalence of Irrationality

India's largest selling pharmaceutical product with a sales of Rs 108 crore is Pfizer's Corex., cough syrup with not much of a therapeutic value. Another equally useless cough syrup is at No.2: Phensydyl of Nicholas Piramal, with sales of Rs 100 crore, another example of triumph of brand promotion and marketing and of unreason over reason.[17] Among other monuments to unreason among the top ten are Liv-52 and Becosules.[18] One of the root causes for irrational prescriptions is the market in the form of irrational fixed dose combination drugs, costly tonics and increasingly food supplements (marketed as "nutraceuticals").

The prevalence of irrational drugs in India in general has been due to:

- Lack of scientific knowledge among prescribers
- Inaccurate diagnosis
- Lack of objective drug information
- Aggressive drug promotion influencing doctors
- Over/under-prescribing by doctors
- Cut-Practice[19].

- Availability of Irrational Drugs in the Market, thanks to poor governance among other things[20]

Some of the common irrational prescription (see box below on "Ten Reasons for Irrational Prescribing") and treatment practices include:

- Prescribing antibiotics for ailments like diarrhoea or viral infection where they are useless, thus causing antibiotic resistance by the body when needed for dangerous diseases.
- Prescribing combination products where one medicine is sufficient.
- Prescribing unnecessary expensive vitamins or tonics, virtually regardless of the condition being treated.
- Prescribing expensive new drugs in preference to established, less expensive ones.
- Ordering of unnecessary investigations.

Poor governance, poor regulation, poor ethics and lack of application of mind by medical professionals combined with greed of drug companies – the one reinforcing the other - has led to this therapeutic chaos and nihilism masquerading as healing science. The case of nimesulide below shows how bad medicine and bad knowledge is sought to be legitimised by using opinion polls, among other fanciful devices!

Box 2:Ten Reasons for Irrational Prescribing

1. The belief of a pill for every ill.
2. The more the merrier, combinations work better, and the belief in shotgun therapy.
3. I have to cover all possibilities.
4. The latest is the best (latest antimalarials, antibiotics, analgesics, etc.)
5 Costlier is better, especially with poor quality drugs in the market.
6. My professor said so…
7. The MR (medical representative) said so…
8. The patients demand it (or, I will lose my practice…) …
9. In my experience...
10. The more I write the more I earn…

Some Frequently Abused Drugs in India, Thanks to their Large-Scale Prescription

1. Vitamins. 2. Digestives. 3. Cough expectorants. 4. Antibiotics. 5. Injections of all kinds. 6. Analgesics. 7. Blood (as transfusions).

-Observations of a practising physician doing rational practice

A wrong repeated several times and especially by seniors in the profession who are seen to have social and professional legitimacy becomes the normative practice; and honest rational deviants are seen as impractical fools unable to find their way in the real world (see Box 3*)*.

We consider some specific cases of how irrational drugs are legitimised and propagated by both regulatory authorities in India and by drug companies, Indian and international.

Case of Nimesulide: Reluctant Rulings

Nimesulide was discovered by an American company, 3M Pharmaceuticals, but never got approval for use in the US, Canada, Britain, Australia, New Zealand and 140 other countries around the world.

The case of how nimesulide has been allowed to continue in India is indicative of how decisions regarding problem drugs are taken in India. In India, marketing approval for the drug was granted in 1994 for painful inflammatory febrile disorders but it is being promoted as first line antipyretic therapy.

Numerous studies have established the life-threatening adverse events with nimesulide such as hepatotoxicity, renal toxicity, severe skin reactions including fixed eruptions, gastrointestinal toxicity, potentiation of seizures, potentiation of colitis in passive cigarette smoking. Studies have also shown that nimesulide should not be used as the primary mode of treatment as an antipyretic or analgesic, especially in children, for whom much better and safer choices are available. There is no reason for selecting nimesulide as the first drug of choice for fever or pain.

Subsequently, nimesulide was banned in Spain and Finland in 2001 on reports of its hepatotoxicity. Even in Sri Lanka and Bangladesh, nimesulide is not allowed to be marketed. Around August 2003, the European Medicine Evaluation Agency (EMEA) had banned the use of nimesulide in all the 25-member countries. Even in adults, its use has been restricted to acute pain, osteoarthritis, and dysmenorrhoea. Its use for fever is not permitted. Also, it cannot be used for dental diseases such as pain and inflammation. Its topical form is to be used only for relief of pain due to sprains and acute inflammation of tendons due to injury (traumatic tendonitis) only.

Box 3: Specialists and Inappropriate Prescription

Prescription patterns reflect the frequency of visits by medical representatives, particularly high among medical teachers and busy consultants. Studies suggest that attendance at 'scientific' company-sponsored symposia and acceptance of pharmaceutical companies' publications "alter physicians' prescribing practices and patient care", often resulting in their prescribing inappropriate and expensive drugs even for unapproved indications. All doctors working for the Bangladesh government, including professors of medical institutes, are free to indulge in unlimited private practice. Doctors in a position of authority and influence are encouraged by drug companies to attend company-sponsored seminars in their own countries and abroad.

This practice is rife in industrialized countries. One survey in Canada revealed that 17 per cent of doctors had their travel expenses and conference fees paid by pharmaceutical companies and 3 per cent were presented with computer equipment. Unfortunately, many symposium proceedings are later published in well-known journals with financing from the same sponsor; the British Medical Journal, the Lancet, the New England Journal of Medicine and the Journal of the American Medical Association are notable exceptions to the plethora of medical journals, which publish drug companies' symposium proceedings (see table below).

These journals are then distributed free to other, less senior doctors to make sure that they too prescribe the new, often dubious products. Such publications also promote untested new technology. The prescriptions issued by senior physicians are immediately copied by juniors, and gradually by general practitioners and by unqualified doctors. This tendency is pronounced in Third World countries.

Source: Chowdhury, Zafrullah. *The Politics of Essential Drugs.* Vistaar Publications, New Delhi, 1995, pp.124-126.

Box 4:Number of Symposia Proceedings Published in Selected Journals

Journals	*Number of symposia proceedings published 1966-1979*	*1980-1989*
American Journal of Cardiology	3279	0
American Heart Journal	25	0
Hypertension	0	17
Circulation	3	11
American Journal of Medicine	18	67
American Journal of Obstetrics	0	10
British Journal of Anaesthesia	5	11
Cancer	6	13
Journal of Allergy Immunology (Clinical)	1	11
Kidney International	5	23
Transplantation Proceedings	6	56
British Medical Journal	0	0
New England Journal of Medicine	0	0
Lancet	0	0
JAMA	0	0

Source: Bero, L.A. et al. 'The Publication of Sponsored Symposiums in Medical Journals'. *New England Journal of Medicine*, October 15, 1992.

Earlier, the Drugs Controller General of India (DCGI), earlier in his response to a Public Interest Litigation (PIL), filed by Social Jurist, an NGO, seeking a ban on nimesulide,

informed the Delhi High Court that there was no reason to ban the drug in India. There are over 70 brands of nimesulide paediatric suspensions in the Indian market, including Nise of Dr. Reddy's Labs and Nimulid of Panacea Biotec. The two account for more than 50 per cent of the market. And the nimesulide market then was of the order of Rs 700 crores with mark ups over 1500 per cent. Since then prices have come down, though not the share of nimesulide sales of various companies.

The European decision instead of turning many medical faces red in India, left them unfazed by and large. In a peculiarly Indian twist to evidence-based medicine, on the basis of an "opinion poll" among just 50 doctors of the over 400,000 doctors, the Indian Medical Association (IMA), Delhi branch, came to the conclusion that nimesulide was "safe and effective for all age groups starting with day one to over 60 years" for a variety of conditions, including fever. In the wake of media reports on the drug during 2003, the Indian Academy of Paediatrics (IAP) also advocated continued use of nimesulide by Indian children. Earlier the IAP, after an analysis of published literature on prospective randomised controlled trials on the drug, had opined, "Nimesulide is as safe or unsafe as other anti-pyretic drugs." The IAP said that the drug can be prescribed for short-term use in children, for less than 10 days of treatment. Data on the effect of the drug in children below six months being limited, no definite conclusions could be drawn on the effect of such use, IAP told the DCGI.

Even as the controversy over the safety of the non-steroid anti-inflammatory drug (NSAID) nimesulide raged on, Dr Reddy's Labs (DRL)and Nicholas Piramal India, two of the leading manufacturers of this drug in India,- decided to withdraw some of their brands containing nimesulide from the market. DRL withdrew all fixed-dose combinations of nimesulide (Nise Spas and Nise Spas DS, Novigan N, NIAP and Nise MR) and Nicholas Piramal India withdrew its nimesulide tablets for adults from the market. Dr Reddy's Nise brand is the market leader in the nimesulide-based NSAID segment and is still available. Also available still is Nimulid, another leading brand marketed by Panacea Biotec, another leading manufacturer of this drug.

DCGI prayed that the matter be referred to the DTAB (Drug Technical Advisory Board) since it is the constitutional body with expertise on drugs. The DTAB (with 5 out of 10

members attending the meeting) informed the court that since "no adverse reports had been received from within the country," there was no need to ban the drug. On the specific question of use in children, the DCGI filed a false affidavit to say that its use in children was allowed in Switzerland and Belgium. The fact is that it was never permitted in these two countries. Social Jurist filed documents from the drug regulators of Belgium and Switzerland but the Delhi High Court ignored the submission. Ultimately the High Court refused to intervene, which meant that nimesulide could continue to be sold; and indeed it continues to be sold in the Indian markets.

On the question of nimesulide FDCs with other agents, the DCGI informed the Court that the FDCs were launched without its approval due to licences issued by state drug controllers; that FDCs with paracetamol or tizanidine or chlorzoxazone had been in the market for some time and were being patronised by the medical profession and no adverse reports had been received; hence they may be "regularised" (i.e., legally permitted post-facto). On other FDCs, the DTAB will be asked to review. So far, even after the lapse of more than three years, nothing has happened and new FDCs with three agents have been launched since.

Around May 2003, the Drugs Controller General of India (DCGI) directed nimesulide manufacturers to withdraw the paediatric “drops” formulation from the market. Those concerned at the turn of events felt that withdrawing drops alone and letting nimesulide suspensions off the hook would defeat the purpose of a ban. As the “drops” are only a diluted form of the suspension, why cannot the government ban the entire drug, these experts argued. By directing a ban on nimesulide drops, the DCGI did accept that the drug had serious side-effects. Based on the suggestions of the DTAB (Drug Technical Advisory Board), the DCGI also asked that manufacturers to print a cautionary note on the label or the package insert saying that “co-administration with other potentially hepatotoxic drugs should be avoided.”

The November 2002 issue of *Current Science* (‘Drugs control: A slippery slope’, Vol. 83, No. 9, 10 Nov 2002) raised other fundamental questions in its editorial:

> The responsibility for ensuring, to the extent possible, the safety of widely used drugs rests with the Drugs Controller of India, whose office falls within the broad sphere of responsibility of the Ministry of Health. Does the Drugs Controller's office have the necessary wherewithal to make scientifically valid decisions on drugs? In an area whose

technical complexity grows with each passing day, can an office functioning under a ministry, not noted for its scientific strengths, efficiently and credibly discharge its mandate? Can an office steeped in a 'ministerial culture' resist the pulls and pressures of competing pharmaceutical houses? The present attack on nimesulide and the publicity given to reports of its liver toxicity in children must undoubtedly have its origins in the strategic marketing wars that drug companies are prone to wage.

After all, the literature reports on the adverse reactions of nimesulide and other non-steroidal antiinflammatory agents have been known for some time. If there was reason for concern it is incumbent on the Drugs Controller to make these public, rather than to respond only when the popular press raises the issue, stridently. It is also necessary for manufacturers of nimesulide, particularly those with the muscle of research and development departments behind them, to provide convincing data that toxicity in local populations is not significant.

Banning of Cox-2 Inhibitors: Rofecoxib, Valdecoxib, Celecoxib, etc.

Internationally, a whole group of 'block buster' drugs have been in serious trouble.[21] These include rofecoxib ('Vioxx'), celecoxib ('Celebrex'), valdecoxib ('Bextra'), atoravastin ('Lipitor'), etc. As of writing there is enough evidence to doubt the safety of a host of cyclooxygenase (COX)-2 inhibitors.[22]

The case of rofecoxib is instructive in terms of how a leading MNC drug company with a block buster does anything to ensure its continued presence in the market, how research studies are reported and interpreted selectively and how meta-analyses can be used to support contrary positions, and how the US FDA acts ever so haltingly and indecisively (and India's drug authorities are 'conservative' in comparison). It is also instructive in terms of legislative oversight that can put pressure for the better.

Rofecoxib was first marketed by Merck in 1999. The following year, a randomized trial[23] in arthritis patients (VIGOR, the Vioxx GI Outcomes Research study) revealed increased rates of adverse cardiovascular events among patients who took rofecoxib compared with patients who took naproxen. Merck researchers attributed this difference to cardioprotective effects of naproxen, aggressively defended rofecoxib's safety with a series of meta-analyses and retrospective studies, and spent hundreds of millions of dollars marketing rofecoxib to physicians and consumers. More than 80 million people took the drug, which might have caused large numbers of excess serious cardiovascular events.

Merck's eventual decision to withdraw - effective September 30, 2004 - Vioxx from the market was based on new data from a trial called the APPROVe (Adenomatous Polyp Prevention[24] on VIOXX) trial. In the APPROVe trial, Vioxx was compared to placebo (sugar-pill). The purpose of the trial was to see if Vioxx 25 mg was effective in preventing the recurrence of colon polyps. This trial was stopped early because there was an increased risk for serious cardiovascular events, such as heart attacks and strokes, first observed after 18 months of continuous treatment with Vioxx compared with placebo. In addition to its own studies, Merck apparently received information about new research by the FDA that supported previous findings of increased risk of heart attack among rofecoxib users. US FDA analysts estimated that Vioxx caused between 88,000 and 139,000 heart attacks, 30 to 40 per cent of which were probably fatal, in the five years the drug was on the market.

The Lancet published a meta-analysis of the available studies on the safety of rofecoxib (Jüni *et al*., 2004). The authors concluded that, owing to the known cardiovascular risk, rofecoxib should have been withdrawn several years earlier. *The Lancet* published an editorial, which condemned both Merck and the US FDA for the continued availability of rofecoxib from 2000 until the recall. Merck responded by issuing a rebuttal of the Jüni *et al*. meta-analysis (Merck and Co., 2004). In 2005, advisory panels in both the U.S. and Canada encouraged the return of Vioxx to the market, stating that Vioxx's benefits outweighed the risks to patients. The advisory panel's 17-15 ruling allowed the drug to return to the market despite being found to increase heart riskeven as public interest groups found evidence of "stacking" and conflicts of interest among the Committee members.[25]

Cardiovascular data from placebo-controlled studies of all three available COX-2 inhibitors were published in 2005.[26] After reviewing these and other findings, an FDA advisory committee recommended that all three COX-2 inhibitors be allowed to remain on the market with expanded safety warnings and without advertising directed at consumers. The vote on celecoxib was a decisive 31:1, but the votes on rofecoxib and valdecoxib were close. Rofecoxib *has not been returned* to the market however. The Government of India prohibited sales of rofecoxib and its formulations from December 13, 2004.

Valdecoxib was eventually withdrawn on April 7, 2005, after a US FDA request asking Pfizer to voluntarily remove Bextra (valdecoxib) from the market – a decision based on an increased incidence of severe skin reactions compared with other nonsteroidal anti-inflammatory drugs (NSAIDs) and evidence of increased risk of cardiovascular malfunction. This decision appeared to validate the analysis of Dr. David Graham, a medical expert at FDA. Graham became a whistleblower[27] rather than keep silent about FDA approved drugs that he perceived as killing people--among these, Vioxx. Dr. Graham's recommendations--which were based on the evidence-- were rejected by his bosses at the FDA and by FDA's expert advisory committee, which voted to allow the continued marketing of painkiller drugs that were shown to induce fatal heart attacks and strokes, in February 2005. *The New York Times* reported that 10 of those 32 panelists on FDA's advisory committee who swung the votes had ties with those drugs' manufacturers - Pfizer and Merck. It was later revealed by the Center for Science in the Public Interest, that, in fact, 27 of the 32 panelists had financial ties to drug manufacturers.[28]

The Government of India notified a ban on the manufacturing and marketing of valdecoxib formulations in the country effective from July 25, 2005 not before frenetic lobbying by pharma companies in India to rescind the ban on rofecoxib and desist from any prohibition on valdecoxib. Valdecoxib was subsequently withdrawn both from European markets too. According to the two regulatory agencies, the U.S. Food and Drugs Administration (USFDA) and the European Medical Evaluation Agency (EMEA), valdecoxib poses unacceptable (a) cardiovascular risks, (b) serious, unpredictable, life-threatening skin reactions, and (c) valdecoxib has no advantage compared to other NSAIDs.

Celecoxib (brand Celebrex) is the only COX-2 inhibitor still available; as with all prescription NSAIDs, it now carries a boxed warning regarding cardiovascular and gastrointestinal risks. However the US FDA issues an alert in March 2005 saying: “Based on emerging information, including preliminary reports from one of several long term National Institutes of Health (NIH) prevention studies, the risk of cardiovascular events (composite endpoint including MI, CVA and death) may be increased in patients receiving Celebrex. FDA will be analyzing all available information from these studies to determine whether additional regulatory action is needed.”

The Drug Controller General of India (DCGI) has asked drug companies to carry a warning on the label of selective Cox-2 inhibitors: "This drug should be used with caution in patients from Coronary heart Disease (CHD)/Cardiovascular Disease".

In August 2005, a Texas jury awarded a US$253 million settlement to the widow of a man who died of an arrhythmia (rapid heart beats) while taking rofecoxib. Three months later in New Jersey, Merck was found not liable for an MI that occurred while the plaintiff was taking rofecoxib. Thousands of rofecoxib-related lawsuits are still pending.[29]

Finally, in December 2005, the *New England Journal of Medicine* raised a new 'concern' (N Engl J Med 2005 Dec 29; 353:2813) that study authors might have deliberately withheld data about myocardial infarctions when they reported results from the critical 2000 VIGOR trial, which established rofecoxib's gastroprotective qualities but also suggested that it might cause excess cardiovascular morbidity.[30]

What then is the modus vivendi of banning a drug or retaining it: its international practice or local adverse effects? If it is the former nimesulide has not been licensed for public use in its originator countries. But it has continued to be used in India, thanks to dubious opinion polls and a reluctant regulatory authority. Whereas Coxibs where banned with little or no push from anybody using their withdrawal in USA as a precedence. And then several other harmful drugs like analgin continue to exist even though they have been withdrawn from the first world countries. .

Dexorange: Top-Selling Anemia Preparation Earlier Containing Haemoglobin[31]

An outstanding example of a patently irrational drug is of Dexorange. This formulation is used for treatment of one of the most common and serious health problems of people, anemia. It is one of the top selling preparations in India with a Moving Annual Total in retail sales (ORG Nielsen October 2003) of Rs. 57 crore. Its overall rank in the top 300 brands was No 16 in 2003 and it outperformed some of the rational preparations for treatment of anaemia which do not even figure in the top 300 brands. Till 2000, this company for over a decade and a half was adding minute amounts of haemoglobin

obtained from slaughterhouse under unhygienic conditions to its even otherwise irrational formulation of iron.

The amount of haemoglobin added to the preparation was such as to provide a meager additional 2-3 mg of iron per 15 ml.

The addition of haemoglobin of animal origin to an iron preparation is without parallel in the pharmaceutical sector worldwide. No other formulary mentions it, and no other country allows it. How was this preparation passed for marketing in India? The answer is not clear. But it took years for the drug regulatory authorities to notice the irrationality of this top selling preparation and declare a ban on haemoglobin preparations and wrote:

> haemoglobin obtained from animal blood could be unhygienic and such preparations are needed to be taken in extraordinary high volume to deliver the recommended level of iron in anaemic cases and thus lacks therapeutic rationale.

This particular preparation still contains an iron salt, which is less efficiently absorbed, in a concentration that is low, and is still marketed at a price that is extravagant. The cost of treating iron deficiency anaemia with this preparation can be up to Rs. 600 per month, against the cost with a simple iron-folic acid preparation that should cost Rs. 9 per month.

The case of the consistent marketing success of Dexorange is not a mere example but stands as an damning indictment of the state of affairs in the pharmaceutical sector, the government and the prescribers, which has put the interests of the voiceless patient/consumer to the background. If after more than a decade during which this company marketed this top-selling preparation adding animal haemoglobin from slaughterhouse blood, the government finds that this addition was not justified, and in fact hazardous, why did it allow a preparation like this to be marketed in the first place? Are the drug regulatory authorities so deficient in scientific understanding that they cannot evaluate a simple preparation for anaemia? If they slipped up, why did it take a drug approved in 1971 to get banned in 2000, 30 years of animal blood consumption by the unfortunate public of India?

Letrozole Affair

Over 400 women were allegedly used as “guinea pigs” by some researchers to test anti-cancer drug, Letrozole, for curing infertility through induction of ovulation. The clinical trials allegedly took place without the permission of the Drug Controller General of India

at private clinics in places like Delhi, Nagpur, Hyderabad, Kolkata and Jodhpur. Letrozole belongs to Schedule G of the Drugs and Cosmetics Rules and can be sold only against prescriptions from cancer specialists. Based on documents submitted by the innovator of the drug, Novartis, US Food and Drug Administration and British Medicines and Healthcare Products Regulatory Authority have labeled it as embryotoxic and fetotoxic at miniscule doses. [See news report "Doctors in India prescribe unapproved fertility drug" in the *British Medical Journal*, BMJ 2003; 327:768 (4 October)]

Case of Zinc, etc., in Haematinic Preparations [32]

On the recommendations made by the Drug Technical Advisory Board (DTAB), the Drug Controller General of India (DCGI) had directed the state drug authorities in 1999 not to allow the manufacture of iron preparations containing zinc, amino acids and vitamins other than folic acid and vitamin C from August 31, 2000. Zinc, among other things, is known to interfere with the absorption of iron; excess zinc in pregnant women is known to increase premature delivery and stillbirth.[33] The DCGI directive had further stated that haemostatic preparations containing ferrous or ferric salts should provide elemental iron between 25 mg to 30 mg prophylactic use and between 60 mg to 100 mg therapeutic daily use. The DTAB, with probably some of the best brains from amongst pharmaceutical and medical sciences in this country, is considered to be the supreme authority in the country to advise the office of DCGI. Yet, the DCGI informed the state drug controllers after almost one year that the whole matter is being referred to the expert committee of DTAB and recommendations of this committee would be examined by DTAB for taking a *final* view in this matter. Until then, the instructions issued by DCGI in respect of iron preparations are to be kept in abeyance. The change of mind of the DCGI was music to 300-odd drug companies, including Franco Indian, Raptakos Brett, Parke Davis, etc which are making these preparations at huge profits for several years. There are majors also in this business. These companies had built their brands over the years and a sudden halt of the sales of these products would definitely hit their bottom lines. It does not take a whole lot to guess what must have happened behind the scenes.

III

Knowledge Legitimating Processes in Public Health Policy Making

We discuss below cases of knowledge legitimation in public policy making that should not have been legitimised in the first instance: legitimation that often started with a wrong practice, often irrational and unscientific, or a piece of research wrongly interpreted because of vested interests or plain incompetence and extrapolated to large scale populations. Knowledge legitimation can also happen by having the correct knowledge and analysis but an unwillingness shown by academics/medical professional bodies/regulatory authorities to stand up and be counted for integrity and the straight narrow path of scientific common sense. We take three examples: vaccination practices in rabies, polio and hepatitis B - all 3 cases symptomatic of bad science and/or bad policy making and/or vested interests or all. And therefore symptomatic of the illegitimacy of knowledge as codified by repeated irrational practice. "What I say three times is true."

Be forewarned that it is not our plaint that this is what happens all the time – sometimes there are acceptable extrapolations to public policy spaces.

Case of Rabies Vaccine in India

For long most of us who are above a certain age would remember with dread getting bitten by dogs, mostly because what would follow is a painful 5 cc injection below the abdomen 10-14 times over the next few weeks. . Thanks to the monopoly of the MNCs (Aventis and Chiron) and the apathy of the Indian Government, this obsolete, inconvenient unsafe vaccine continued in Indian public health facilities. It has been available in the private market but has been too costly for most Indians. This "sheep brain vaccine" has from June 2005, thanks to some PILs, been replaced now by cell-culture vaccine (also marketed by MNCs Aventis and Chiron) under the names Rabipur and Verorab).

The cell-culture vaccine, although it means only 5-6 injections, is six-times costlier (around Rs 1500) than the sheep-brain vaccine which used to cost Rs 225 for a dose of 14 injections. The older vaccine was available free of charge in public health facilities whereas the cell culture vaccine being much more costly is available free of charge only

to yellow card holding BPL (Below-the-Poverty-Line) families. The cell culture vaccine comes in ampoules of1 ml to be administered *intramuscularly* (IM). Rabies is very common in India and is often fatal and no vaccine means certain death.

The government can force the drug companies to reduce the prices. Or alternatively, it can insist insist that the 0.1ml injection of the Chick Cell Embryo Vaccine be given *intradermally* (ID) at two sites on the arm at a time on the first, third, 7th, 28th and 90th day of the suspected rabid dog bite. This means a total dose of 0.8 ml of this vaccine in five injection visits to the doctor. This I.D. regimen is now routinely taught to the doctors during their graduation and for many years it has been recommended by the mostly widely used undergraduate *Textbook of Preventive and Social Medicine*, by Park and Park.

Unfortunately, however the two manufacturers have registered the cell culture vaccine in India only for ID use whereas internationally it has been registered for both IM and ID use. Even the WHO recommends ID use. The Government of course has to ensure that 0.1 or 0.2 ml dosages are made available by these companies or arrange to make it in a PSU.

Not being sensitive to cost implications of dosages and therapeutic regimens in a poor country often has its antecedents in poor medicine and poor science.

Polio Vaccine and its Tragic Detritus in India[34]

Polio is a dreaded disease for many a parent, if not only for the lifelong tell tale sign a child has to carry but increasingly for the fatalities it can cause. But consider the programme and the debate surrounding it:

- Two kinds of polio vaccines have been used to fight polio. The first consisting of an injected dose of killed polio virus, was developed by Jonas Salk. The injected polio vaccine was first tested in 1952, and announced to the world by Salk on April 12, 1955. Thereafter, Albert Sabin produced an oral polio vaccine (OPV) using live but weakened (attenuated) virus. Human trials of Sabin's vaccine began in 1957 and it was licensed in 1962.

- OPV introduced in the National Immunisation Programme in 1978-79. This had reduced the number of reported cases of paralytic polio by 80% - from 24,257 in 1988 to 4,793 in 1994.
- Intense campaign using OPV through "Pulse Polio Campaigns" started in 1995 throughout India with the onset of the Global Polio Eradication Initiative (GPEI).
- Problems with OPV surface –the major disadvantage of the live-virus vaccine is that it can result in sporadic cases of polio either from the vaccine itself [vaccine-associated paralytic poliomyelitis (VAPP)] or acute flaccid paralysis from the circulation of the vaccine.
- AFP [Acute flaccid paralysis, the onset of focal weakness or paralysis characterised as flaccid, that is reduced in tone] especially in children less than 15 years old is one of the more unpleasant consequences of OPV.
- Also, vaccine-associated paralytic poliomyelitis (VAPP), discovered in 1950s, appears to increase with intense mass campaigns and repeated pulse polio administration (some children get as much as 10 drops at a time.).
- There does not seem to be any unanimity and clarity as to adverse effects and risks of multiple polio administration.
- Authorities claim drastic reduction of paralytic polio cases from around 5000 per year in 1994, before the launch of the Eradication Drive, to only 66 cases in the year 2005.
- But this is because of a wrong assumption and therefore wrong definition, that all cases of AFP are polio virus related. Up to 1996/97 all reported cases of acute limb paralysis were labeled as polio. From 1997/98 onwards, such cases are labeled as polio only after thorough investigations through stool culture etc. As a result, for example in 1999 only 12 % of such cases were labeled as polio whereas earlier all such paralysis cases were labeled as polio! Naturally with this change in definition, the number of polio cases "came down"!
- Also since every AFP case is still not properly investigated/followed up, there is probably some undercounting of polio cases.
- VAPP cases have been added to the count of polio cases only from 2002! That means the early count of polio cases from 1997-98 (when all cases of AFP were not any more assumed as polio virus related) was an underestimate.

- Polio manifestation has been conflated with AFP only whereas polio virus infection could also end up in abortive poliomyelitis, non-paralytic poliomyelitis. AFP probably accounts for one per cent of the polio infected cases.
- Vaccine failure of OPV due to poor quality, or other genuine inhibiting factors, could be an important cause. Even "good quality" OPV is known to be effective in only 95 of 100 cases administered.
- High incidence of VAPP and vaccine failure seem to put paid to dreams of polio eradication in India.
- There seems to be serological evidence that OPVs are not as effective in warm as in climates.
- Herd immunity was supposed to be a chief advantage of OPV (that is if 60-70 % of the children in a community are given OPV, the rest too get protected). But now some of the earlier chief protagonists of herd immunity have denied any herd immunity effect or even that they ever advocated herd immunity. The point is that the pulse polio method of giving all children one drop simultaneously seems to contradict one claimed advantage of herd immunity.

What is curious in this series of episodes is the uncritical and populist role of the Indian Academy of Paediatrics (IAP). The January 2004 issue of the *Bulletin of Polio Eradication Committee* of IAP (page 3) stated:[35]

> The outcome of our efforts in the coming few months will decide which way the program will go—the small pox way or the malaria way? Already, voices of concern regarding prudence of adopting an eradication approach are emerging from different quarters. Hence, many things are on stake—the reputation of nation, the resolve, commitment, and the patience of its people, the
> strategy and competence of enforcing agencies, and the ambition of scientific fraternity to overpower yet another killer disease in future! And also at stake is credibility and reputation of your own organization IAP…
>
> … (on page 4) India has reached the critical period in our efforts to eliminate the transmission of wild polioviruses. All partners in polio eradication are getting ready for the 'final push' to ensure the achievement of virus elimination during this critical period of December 2003 through April 2004. All States, District and Local Branches of IAP and indeed every member should participate in this historic event of the final push."
>
> ….The Bulletins of the Polio Eradication Committee (of the) IAP raised false hopes time and again that polio eradication was about to occur; at the same time, this committee downplayed the issues of vaccine failure and high incidence of VAPP. Sixty to 75 VAPP cases were expected to occur every year in India. As has been previously stated, this was accepted as a 'price' to pay for polio eradication. However, doctors were advised to keep

> this as a guarded secret—to which the doctors agreed. Later, the number of VAPP cases was found to be much higher and this author raised this issue to the co-convener of the Polio Eradica-tion Committee who stated, "We can dare to disclose the true figures of VAPP only if we have an alternative strategy in place to implement without delay …

More to the point is the wrong advice given by WHO, IAP and other scientific authorities in India often underplaying or suppressing inconvenient data like VAPP, jumping to unwarranted conclusions, repeatedly changing the definition of what is a polio case, and now not even saying we could have been wrong. Indeed it appears a proper evaluation of the efficacy of the vaccine never appears to have been carried out. Did/does anybody took/take the much vaunted informed consent from parents of children to be given pulse polio drops – which means informing about VAPP, AFP and the fact that still the child has only 95 % chance of protection from Polio? Smacks of Akerlofian asymmetry of information and the market for lemons alluded to earlier. Only it is the market for polio drops now. Asymmetry is at best an euphemism that covers the inherent inequity and injustice – in this case the right of rehabilitation and compensation for those afflicted with vaccine related and other forms of paralysis due to a misguided campaign.

"How can WHO give a wrong advice? Is it failure of expertise or influence of vested interests?" Responding to this likely FAQ, Phadke et al respond[36]:

> Perhaps a combination of both. WHO fostered the polio eradication programme when it should have known that this is unattainable. The phenomenon of reversion of vaccine virus into virulent virus; the relative inefficacy of OPV in tropical climate --- all this was known. Yet the Global Polio Eradication Initiative (GPEI) was launched and OPV was recommended for India. Now the international authorities have somewhere realized that eradication of polio and hence cessation of polio vaccination is not possible. Without squarely admitting its mistake, WHO has quietly changed the objective of the polio eradication drive to that of .polio elimination.; which means no cases of polio, but polio vaccination would continue as the polio virus has not been eradicated. WHO has now come up with the ridiculous Post-eradication strategy (a contradictory term!) for vaccination in which it is left to individual countries to decide whether they would give oral, or injectable polio vaccine in the .post-eradication Phase!
>
> That the GPEI was based on manipulation of not only concepts but also of statistics is shown by the way WHO exaggerated the problem of polio. As pointed out earlier, all cases of limb-paralysis or lameness in children were counted as polio, when only a small proportion of them is known to be due to polio. Secondly, while in 1988, there were about 35,000 cases of paralytic polio reported world wide, WHO experts argued that since there is gross under reporting of such cases, the estimated incidence is 10 times more than this figure! After a few years, in 2004, in the Geneva Declaration for the Eradication of Poliomyelitis; this figure of 3.5 lakh estimated cases of poliomyelitis was quietly converted into reported cases. In the document presented to the 57th World Health Assembly in May 2004, WHO experts' statement says that polio is responsible for paralyzing more than 3,50,000 children.
>
> So much for the intellectual integrity of these experts!

Independent experts, commentators in India have been pointing out the basic problems with the Polio Eradication strategy. But no attention has been paid to these dissenting voices.

Hepatitis B Vaccine: Not Counting the Prevalence and Costs Carefully[37]

Hepatitis means inflammation of the liver. It is sometimes caused by germs, including viruses or sometimes by toxic chemicals like alcohol. There are five types of viral hepatitis – called Hepatitis A, B, C, D, E caused by five different viruses: Out of these five types, Hepatitis A, D and E spread from the infected person to others through feco-oral route: that is when viruses in the feces of the infected persons that get mixed up in water or food for others, through flies or hands or through leakage of sewage into drinking water sources, other people get this infection. What is commonly called jaundice is inflammation of liver with attendant fever, nausea, weaknesses, etc. and is self-limiting, with no medicines available, and causes death in rare cases because of liver failure.

Virus subtype B and C are of a different nature. Like the AIDS virus, they spread mostly through infected blood from the infected persons to others or through sexual relations and are far more dangerous than subtypes A, D, E. The point of debate is the proposal by the Government of India to give Hepatitis-B vaccine to all newborns through the National Immunisation Programme. Is this really necessary? Let us review the facts:

- Phadke and Kale[38] show that the usually quoted figure of Hepatitis-B carrier rate of 4.2 % works is actually only 1.42%.[39]
- The WHO has recommended Hepatitis-B vaccination of all newborns only for countries where this carrier rate is more than 2%.
- Hepatitis-B is much more infectious than HIV. However, whereas untreated HIV infection is 100% fatal, in case of Hepatitis-B infection only 10% of infected adults become chronic carriers and the average fatality rate due to hepato-cellular carcinoma is much lower than what has been claimed.
- About 90% of infected infants become carriers. But carriers eliminate the Hepatitis-B infection at an annual rate of up to 2% and the overall incidence of the damage due to Hepatitis-B infection is much less than what is generally believed.

- Newborns who get Hepatitis-B infection at birth from their Hepatitis-B positive mothers have the highest risk of getting the infection and have highest chances of becoming carriers. Prevention of this perinatal (vertical) transmission from Hepatitis-B positive mothers requires that newborns at risk be given the first dose of the vaccine within 12 hours of birth. Hence the WHO, the American Academy of Pediatrics have recommended that for such newborns, the first dose of Hepatitis-B vaccine must be given not later than 48 hours after birth.
- In India, since 77% births take place at home, whereas the first dose of Hepatitis-B vaccine would not be given immediately after birth but 6 weeks after birth with the first dose of the triple vaccine in the National Programme. Hence in this programme 77% of the newborns will not be protected from the mother-to-child mode of infection, which is the most dangerous type of infection.
- If we want to take up Hepatitis-B vaccination programme at all then the Selective Vaccination Strategy should be used like in other low prevalence countries like Japan, U.K. Netherlands. The Selective Vaccination Strategy which consists of identifying the Hepatitits positive mothers through antenatal screening and vaccinating their newborns within 24 hours of birth.
- In India 2-3 % of mothers are Hepatitis-B positive, and this selective strategy would protect by vaccinating only the 3% of the newborns, and this programme would cost one fourth of the Universal Strategy. Out of total new hepatitis-B infections that occur every year, in India, about one-third are from mother to child and by vaccinating just 3% of newborns, we will be able to prevent 33% of these infections!
- This highly cost-effective selective vaccination programme will not be very effective even for control of Hepatitis-B infection (leave aside its eradication from India) unless this coverage is substantially improved. Secondly, it will not eradicate Hepatitis-B infection. But any way even if all newborns are vaccinated in the Universal Vaccination Programme, it will take at least 65 years to eradicate Hepatitis-B infection in India.
- With 25 million babies being born every year in India, even assuming that the cost of Hepatitis-B vaccine per child in this programme to be only Rs. 50/, (i.e. much less than the current price), it would cost Rs. 125 crores annually for the vaccine alone. This is equal to our budget for TB-control programme (the number

one killer of Indian adults) and is almost equal to the combined cost of other 6 vaccines given to infants. The cost-efficacy of this programme is also unfavourable - about Rs. 700 per life year saved compared to around Rs. 20 per life year saved for the measles vaccination.

- Those medical professionals who come in close contact with blood, patients in need of dialysis/repeated blood transfusion and persons exposed to unsafe sexual relations should be vaccinated against Hepatitis-B on a priority along with newborns of hepatitis positive mothers.
- Giving this vaccine to all newborns, that too 6 weeks after birth, is neither effective in preventing the most dangerous, mother-to-child transmission nor is it good economics. It will primarily benefit the manufacturers of this vaccine who have succeeded in convincing a section of the medical professionals through their usual techniques.
- However if budget is available after allocating funds for .Selective Vaccination Programme, the option of vaccination of all other newborns by giving the first dose at 6 weeks can be considered if we use the intra-dermal route for Hepatitis - B vaccination.[40]
- It should be noted that vaccinating all the newborns in the routine immunization programme would protect all newborns from child to child transmission, and not mother-to-child transmission of hepatitis-B infection at least for first 15 years.
- If we vaccinate all newborns then all the female babies would be free of Hepatitis -B infection when they grow up to become mothers and hence the incidence of mother to child transmission would decrease as they start becoming mothers. This effect would start after say 15 years from today and in 40 years, mother to child transmission in India would stop as all child bearing is completed by 40 years of age.
- A number of researchers have claimed that Hepatitis-B vaccination increases the chances of Multiple Sclerosis - a very serious neurological ailment. A study published in 2004,[41] which was conducted by one of the most renowned epidemiologists and based on one the best data bases in Europe, has very much strengthened this suspicion as it found a three fold relative risk of developing Multiple Sclerosis in the population which has received Hepatitis-B vaccine.

Indeed, as Phadke et al observe: "Hepatitis-B vaccination is a classic example of how a particular technological intervention is systematically foisted on the people by the powerful medico-industrial vested interests when there is no scientific rationale for such a use."[42]

IV

Clinical Trials, Research Publications and Conflicts of Interest

'Regulatory Capture': India, a Soft Target for Clinical Trials

Given below are some unethical incidents involving drug trials in India and that happened between the period 1999-2005:[43]

●*Unethical Trials in Collaboration with John Hopkins Scientist***:** New chemical entities called M4N or tetra-O-methyl nordihydroguaiaretic acid and G4N or tetraglycinyl nor-dihydro-guaiaretic acid, discovered in the United States, were unlawfully tested on 26 oral cancer patients at the Regional Cancer Centre (RCC) at Thiruvananthapuram, Kerala, between November 1999 and February 2000. Under unrelenting pressure from the media and NGOs, an unwilling Government was literally dragged to take action. Instead of penalizing the guilty, further research on M4N and G4N was merely suspended for six months! In such cases, the law provides for three months imprisonment for the guilty.[44] Soon after it was tested on 36 mice in the US. The trial of another drug, Foscan, at the RCC has raised hackles as the Food and Drug Administration (FDA) of the US and the European committee empowered to give approval for drugs have more than once blocked clearance. A senior RCC doctor said the issue came to light "when one of the doctors in RCC found out that his patients were being used as guinea pigs for this new derivative, without his consent." "When he protested he was sidelined and he has now approached the State Human Rights Commission and the Kerala High Court for justice." "The team led by the RCC director Dr M. Krishnan Nair instead of removing the tumors on the 24 patients as soon as they were detected, delayed the surgical intervention for varying periods to find out the efficacy of the chemical on cancer cells," he said. In fact, Nair, in a press statement took a joint credit with John Hopkins University in announcing that the drug had been effective in treating certain cancers caused by viruses, the media reports have said. Even as we go to the press, *Frontline* reported:[45]

> More than four years after a petition seeking compensation was filed before the Kerala Human Rights Commission (HRC) by one of the 27 patients involved in the controversial Hopkins-RCC drug trials, a Division Bench of the Kerala High Court quashed it on

November 17, accepting technical objections raised by the Regional Cancer Centre (RCC) and its former Director, Dr. M. Krishnan Nair. They pleaded that as per the Protection of Human Rights Act, the complaint ought to have been filed within one year of occurrence of the event for it to be considered by the Commission. The patient M. Gopalan, therefore, lost his case purely on legal technicalities, with the commission never looking into his complaint of serious ethical violations by the doctors who experimented on him without his voluntary or informed consent.

The HRC had initially rejected the RCC's and Dr. Krishnan Nair's objections. So had a single-Judge Bench of the High Court subsequently. (Another petition filed by Dr. V. N. Bhattathiri is pending before the Commission.)

Gopalan, then a patient awaiting surgery at the RCC, received the last in a series of controversial injections in mid-January 2000. The Division Bench accepted the argument that Gopalan should have filed the complaint within a year of the date of that injection. Perhaps it does not matter any more. Gopalan died a year after filing the complaint.

- Cilansetron, a new molecule of Solvay Pharmaceuticals not approved anywhere in the world was cleared for Phase III trials even though only Phase II trials had been conducted abroad.
- Cilostazol, a product of Otsuka, was cleared by DCGI based on incomplete, inadequate information on adverse effects. Common serious side effects such as angina and myocardial infarction were not even mentioned. Needless to say such omissions can be life-threatening in study subjects.
- The protocol of the drug Tacrolimus submitted by Panacea Biotec and cleared by DCGI was not onlyvague but deficient and defective beyond imagination. It did not even state the Phase of the trial, an elementary requirement, and omitted all important serious adverse effects such as malignancies, cardiomyopathy, lymphoproliferative disorders, etc.
- It appears that some protocols and accompanying documents such as Investigator's Brochures are not even read by DCGI. Otherwise how does one explain approval of patently defective clinical trials? This perception is strengthened by the super speed with which some proposals are cleared: a voluminous protocol on trastuzumab sponsored by Roche was approved within 5 working days. It is humanly not possible to read and analyze the bulky documents in such short period.
- At lease three patients in Hyderabad being tested for the efficacy and safety of recombinant streptokinase have died. Without any independent enquiry, Shantha Biotech that sponsored the trial was washed off its hands by labeling the death of "trial subjects", as they are impersonally called, to "causes other that the use" of the drug! Independent sources place the death toll at eight.

- Dharmesh Vasava, a 22-year-old "volunteer" from Bharuch in Gujarat had died while participating in tests on citalopram sponsored by Sun Pharmaceuticals. According to another participant of the same trial, the subjects were lured with money by agents working for the Company. Such exploitative inducements are both unethical and illegal.
- Erythromycin was inserted into the uteri of 790 poor, illiterate, unsuspecting women in rural West Bengal by two self-styled researchers to test its contraceptive effect without government approval and consent from participants.
- A human trial on Zoniporide, an American new drug, was approved without adequate and mandatory cancer and reproductive studies on animals.

It may sound incredible but animals subjected to experiments in America enjoy more protection than humans in India. A trial done on an animal without approval from the relevant authorities is fined Rs. 110,000 (US$ 2,500) under Animal Welfare Act. In India, more than 1,200 young women have been treated worse than animals," says Dr Gulhati in *MIMS India*.

> Most drug trials in India are conducted without any arrangement for compensation in case of study-related injury disability or even death in human subjects in violation of Indian Council of Medical Research (ICMR) Guidelines.
>
> The investigators for clinical trials are chosen by sponsoring commercial companies. Some such investigators are, or have been, beneficiaries of largesse from the pharmaceutical manufacturers including expensive gifts and air tickets for travels abroad. Neither the regulatory authorities nor the Hospital Ethics Committees seek information from investigators about their financial relationship with drug manufacturers.[46]

Many other instances may be given of well-known companies in India and abroad whose products have failed and continue to fail routinely. As India becomes a "destination" for clinical trials, it is the ordinary person who is at risk in the absence of information in the public domain of clinical trials being conducted. Indeed a new type of colonialism is in the offing as more Indians are being readied as guinea pigs, and as usual some of India's own elite act as instruments of this colonialism. More importantly, the Drug Controller General of India often does a balancing act between public health interests and making Indian industry 'world class' and competitive – goals which could be complementary but in the context of the irrationalities and distortions in the market, it appears to be loaded in the favour of drug industry than people at large. How can we have a "world class" drug industry if the country's chief drug regulatory agency does not apply the highest standards of bioethics in clinical trials - to cite just one area for instance?

Apparently this is true of the US FDA also. Dr David Graham, Associate Director for Science and Medicine in the FDA's Office of Drug Safety, gave relevant evidence to the US Senate Committee on Finance in hearings following the withdrawal of Vioxx and subsequently spoke about the relationship between regulators and industry: [47]

> The FDA has become an agent of industry. I have been to many, many internal meetings and, as soon as a company says it is not going to do something, the FDA backs down. The way it talks about industry is 'our colleagues in industry'… it is rather because the body is entirely geared towards concentrating on approving drugs, doing little once they are on the market

And further added:

> The organizational structure within CDER (Center for Drug Evaluation and Research) is entirely geared towards the review and approval of new drugs. When a CDER new drug reviewing division approves a new drug, it is also saying the drug is "safe and effective." When a serious safety issue arises post-marketing, their immediate reaction is almost always one of denial, rejection and heat. They approved the drug so there can't possibly be anything wrong with it. The same group that approved the drug is also responsible for taking regulatory action against it post-marketing. This is an inherent conflict of interest. At the same time, the Office of Drug Safety has no regulatory power and must first convince the new drug reviewing division that a problem exists before anything beneficial to the public can be done. Often, the new drug reviewing division is the single greatest obstacle to effectively protecting the public against drug safety risks. A close second in my opinion, is an ODS management that sees its mission as pleasing the Office of New Drugs.
>
> The corporate culture within CDER is also a barrier to effectively protecting the American people from unnecessary harm due to prescription and OTC drugs. The culture is dominated by a world-view that believes only randomized clinical trials provide useful and actionable information and that postmarketing safety is an afterthought. This culture also views the pharmaceutical industry it is supposed to regulate as its client, over-values the benefits of the drugs it approves and seriously under-values, disregards and disrespects drug safety.

Clinical Trials and 'Tainted Evidence'

A study published in *JAMA* (2003) to explore whether there was an association between funding and conclusions in randomized drug trials reflects treatment effects or adverse event concluded that trials funded by for-profit organizations may be more positive due to biased interpretation of trial results. "Readers should carefully evaluate whether conclusions in randomized trials are supported by data."[48]

In another study by Bhandari M. etal of 332 randomized trials (consisting of 158 drug trials, 87 surgical trials and 87 trials of other therapies) reported: "In 122 (37%) of the trials, authors declared industry funding. An unadjusted analysis of this sample of trials

revealed that industry funding was associated with a statistically significant result in favour of the new industry product (odds ratio [OR] 1.9, 95% confidence interval [CI] 1.3-3.5). The association remained significant after adjustment for study quality and sample size (adjusted OR 1.8, 95% CI 1.1-3.0). There was a nonsignificant difference between surgical trials (OR 8.0, 95% CI 1.1-53.2) and drug trials (OR 1.6, 95% CI 1.1-2.8), both of which were likely to have a pro-industry result (relative OR 5.0, 95% CI 0.7-37.5, p = 0.14)," and concluded that "Industry-funded trials are more likely to be associated with statistically significant pro-industry findings, both in medical trials and surgical interventions."[49]

A more recent study of outcomes of major cardiovascular clinical trials funded by for-profit and not-for-profit organizations concluded: "Recent cardiovascular trials funded by for-profit organizations are more likely to report positive findings than trials funded by not-for-profit organizations, as are trials using surrogate rather than clinical end points. Trials jointly funded by not-for-profit and for-profit organizations appear to report positive findings at a rate approximately midway between rates observed in trials supported solely by one or the other of these entities."[50]

In a study comparing Cochrane reviews with industry supported reviews, it was found that "Industry supported reviews of drugs should be read with caution as they were less transparent, had few reservations about methodological limitations of the included trials, and had more favourable conclusions than the corresponding Cochrane reviews."[51]

The list of such studies showing the lack of even a pretense to objectivity is now numerous. Indeed such studies raise the question of the uncertain foundations of knowledge so constructed.

It is because of such evidence, some editors of reputed medical journals[52] have been convinced for sometime now that medical journals are the marketing arm of pharmaceutical companies. In a joint statement titled, "Sponsorship, Authorship, and Accountability" in September 2001, 13 of the world's leading medical journals accused drug companies of distorting the results of scientific research for the sake of profits. *The Lancet, the New England Journal of Medicine, the Journal of the American Medical*

Association and other major journals accused the drug giants of using their money - or the threat of its removal - to tie up academic researchers with legal contracts so that they are unable to report freely and fairly on the results of drug trials. "We are concerned that the current intellectual environment in which some clinical research is conceived, study subjects are recruited, and the data analyzed and reported (or not reported) may threaten this precious objectivity."[53]

Scientists, often from cash-starved university departments, noted the statement, may be prevented from having access to the raw data gathered in the trial which would tell them how well or not the drug worked and whether there were side-effects. They may be given no say in the way the trial is designed and they may have only limited participation in interpreting the results. "These terms are draconian for self-respecting scientists, but many have accepted them because they know that if they do not, the sponsor will find someone else who will. And, unfortunately, even when an investigator has had substantial input into trial design and data interpretation, the results of the finished trial may be buried rather than published if they are unfavourable to the sponsor's product," said the commentary which ran in 12 of the 13 journals.

According to Richard Horton, editor of *The Lancet*, and one of the signatories, "The patient should know who is in control of the study. Are you - my doctor or the scientist doing the study - in control or is the pharmaceutical company in control? They are never told anything of the sort. At the moment, informed patient consent is a fabrication."[54]

Academic scientists had little choice but to accept the restrictions imposed on them, the statement went on to note, because they knew that otherwise the funding they needed for research would go to the increasing number of private contract research organizations (CROs). These organizations in the USA received up to 60% of the research grants handed out by pharmaceutical companies in recent years.

> As CROs and academic medical centers compete head to head for the opportunity to enroll patients in clinical trials, corporate sponsors have been able to dictate the terms of participation in the trial, terms that are not always in the best interests of academic investigators, the study participants, or the advancement of science generally.

The editors decided to take action, henceforth, by requiring all authors to disclose details of their own and the sponsoring pharmaceutical company's roles in the study. Some

editors would be asking for a signed declaration from the author that they accept responsibility for the trial. If the company has sole control of the data, the journals will not publish the study.

> …contracts should give the researchers a substantial say in trial design, access to the raw data, responsibility for data analysis and interpretation, and the right to publish the hallmarks of scholarly independence and, ultimately, academic freedom. By enforcing adherence to these revised requirements, we can as editors assure our readers that the authors of an article have had a meaningful and truly independent role in the study that bears their names. The authors can then stand behind the published results, and so can we.[55]

Elsewhere Richard Horton, editor of the *The Lancet*, wrote that "journals have devolved into information-laundering operations for the pharmaceutical industry."[56] Advertisements, however, are the least form of corrupting influence according to Richard Smith,[57] the former editor of *British Medical Journal (BMJ)*. It has more to do with sponsored clinical trials and the reporting of clinical trials – seen by the public at large as a neutral form of evidence. "Readers see randomised controlled trials as one of the highest forms of evidence. A large trial published in a major journal has the journal's stamp of approval (unlike the advertising), will be distributed around the world, and may well receive global media coverage, particularly if promoted simultaneously by press releases from both the journal and the expensive public-relations firm hired by the pharmaceutical company that sponsored the trial. For a drug company, a favourable trial is worth thousands of pages of advertising, which is why a company will sometimes spend upwards of a million dollars on reprints of the trial for worldwide distribution. The doctors receiving the reprints may not read them, but they will be impressed by the name of the journal from which they come. The quality of the journal will bless the quality of the drug." (See also box below on *Examples of Methods for Pharmaceutical Companies to get the Results they want from Clinical Trials*). And Smith continues:

> Fortunately from the point of view of the companies funding these trials -- but unfortunately for the credibility of the journals who publish them -- these trials rarely produce results that are unfavourable to the companies' products. Paula Rochon and others examined in 1994 all the trials funded by manufacturers of nonsteroidal anti-inflammatory drugs for arthritis that they could find.[58] They found 56 trials, and not one of the published trials presented results that were unfavourable to the company that sponsored the trial. Every trial showed the company's drug to be as good as or better than the comparison treatment.

Box 5: Methods Used by Pharmaceutical Companies to Get Desired Results from Clinical Trials

- Conduct a trial of your drug against a treatment known to be inferior.
- Trial your drugs against too low a dose of a competitor drug.
- Conduct a trial of your drug against too high a dose of a competitor drug (making your drug seem less toxic.)
- Conduct trials that are too small to show differences from competitor drugs.
- Use multiple endpoints in the trial and select for publication those that give favourable results.
- Do multicentre trials and select for publication results from centres that are favourable.
- Conduct subgroup analyses and select for publication those that are favourable.
- Present results that are most likely to impress—for example, reduction in relative rather than absolute risk

Source: Richard Smith. 'Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies', *PLOS, Vol 2*, Issue, May 2005 and at <http://medicine.plosjournals.org>. Smith is a former editor of *BMJ*

Need for Clinical Registry

We have already mentioned above how India has become a destination for "regulatory capture" a soft target for clinical trials by CROs (Contract Research Organisations) and drug researchers, producing at best what could be termed as biased research emanating from tainted evidence and violating human rights of poor patients in the worst possible way. If anything this indicates a need for a clinical trial registry in the public domain and India's regulatory authorities may well wake up now than later. In the United States, the Food and Drug Administration Modernization Act requires that all trials on life-threatening diseases be registered into <http:/ClinicalTrials.gov>, a register maintained by the National Institutes of Health, yet only 48% of industry-sponsored trials were registered during the initial period of the law's implementation.[59] Selective reporting of results to benefit drug company interests rather than public health seems to be happening: In 2004, GlaxoSmithKline settled a US$2.5 million lawsuit for suppressing trial results showing that its antidepressant paroxetine (Paxil) increased suicidal ideation in children. As part of the settlement, GSK agreed to set up a public register of all clinical trials on all of its drugs.[60] This is contrary to a longstanding understanding, and one supported by regulatory agencies world over, that clinical trial results are company property and commercially confidential. IP and WTO need not come in the way of transparency – the whole point of IP, at least the way drug industry has advocated it, is to let everybody see what you are doing.

Again more recently, Merck and Pfizer have been criticized for withholding results showing increased risk of heart disease from COX-2 drugs such as rofecoxib (brand name Vioxx), which was withdrawn from the market because of these risks.[61]

Drug companies, driven by economic pressures, conduct often post-approval studies.[62] Merck and Pharmacia did extensive post-approval studies to show that their arthritis pain medications, Vioxx and Celebrex, were easier on the stomach than older, cheaper painkillers. Merck's study, involving more than 8,000 adults, showed Vioxx causes fewer stomach complications than the painkiller naproxen, but also found it increases the risk of heart attacks. Both facts were widely reported in medical journals and the media, and the company stepped up promotion of the drug's safety since the FDA added that information to the drug's label. Finally Merck's Vioxx was taken off because of the fortuitous results of an efficacy study not a safety study (see box below "It is better to kill a drug than kill a patient".)

Box 6: "It is better to kill a drug than kill a patient"

…More importantly, there were no attempts to design and carry out large safety studies to prove or disprove the link of Vioxx to heart attacks. Apparently, a 30,000 patient study had been announced in November, 2001 but never started. Last week, New York Times reported that Merck had considered a cardiovascular outcome study, but decided that it would send the "wrong" marketing and public relations signal. "At present, there is no compelling marketing need for such a study," said a slide prepared for a meeting of senior executives. "Data would not be available during the critical period. The implied message is not favorable." It is regrettable that scientific decisions on patient safety are influenced by perceived marketing and public relations concerns. In my opinion, it is better to kill a drug than kill a patient.

It is important to note that the APPROVE study which conclusively proved the increased risk of Vioxx was not a safety study – it was an efficacy study, designed to add another indication for Vioxx treatment. It was not large enough to detect a heart attack risk – that it did find a risk was a lucky break for patients, but this is not what it was designed to do.
The failure to conduct large long-term safety studies subjected millions of patients over 4 years to a drug whose safety had been questioned by the FDA even before its approval. This is not the proudest chapter in drug approval in the US…

--Gurkirpal Singh, MD, affidavit before US Senate reviewing the science of Cox-2 inhibitors and the link of rofecoxib to heart attacks[63]

Pfizer tried hard to continue marketing its block buster Lipitor (see also Box 6 below, "Pfizer Fraud Alleged"). Likewise, Pharmacia circulated preliminary results suggesting that its study of more than 8,000 patients showed that Celebrex was easier on the stomach than ibuprofen. But, in the end, the FDA ruled that the study showed no such benefit and

the *British Medical Journal* criticized the company for "distributing overoptimistic short term data" from its study.

Box 7: Pfizer Fraud Alleged

Pfizer misled consumers into using its anti-cholesterol drug Lipitor despite the absence of evidence from clinical trials that the drug or others in its class are of any benefit to large segments of the population, according to a consumer class action lawsuit filed against the world's largest drug maker in October.

According to Steve Berman, the lead attorney for the proposed class, Pfizer promoted Lipitor by claiming it prevents heart disease in women and the elderly, even though no clinical test has established such a benefit. The lawsuit alleges that Pfizer engaged in a massive campaign to convince both doctors and patients that Lipitor is a beneficial treatment for nearly everyone with elevated cholesterol, even though no studies have shown it to be effective for women and those over 65 years of age who do not already have heart disease or diabetes.

Lipitor is in the class of cholesterol-lowering drugs called statins and it is the best-selling drug in the world, with sales in 2004 of more than $10 billion. "The idea that lowering cholesterol always reduces the risk of heart disease has become the conventional wisdom, which drug companies like Pfizer have taken great pains to promote," says Dr. John Abramson, clinical instructor of ambulatory care at Harvard Medical School and author of Overdosed America: The Broken Promise of American Medicine. "But for women under 65 and people over 65 with no history of heart disease or diabetes, the evidence just isn't there. Millions of women and seniors are spending huge sums to take Lipitor every day despite a lack of proof that it's doing anything beneficial for them, and may actually be harming the elderly."

Source: <http://www.multinationalmonitor.org/mm2005/092005/names.html>
September/October 2005 - Volume 26 - Numbers 9 and 10.

Elsewhere, it has been reported that, "Five out of six systematic reviews published in the last two years have shown that research that is sponsored by a drug manufacturer is more likely to yield a positive result for the company's product than research that is independently sponsored."[64]

These studies are hardly supervised either by the FDA in USA or by the companies themselves. The studies themselves are not risk free and side effects come to light only when a drug is used widely. Doctors who test post-approval drugs are more likely to prescribe them to their patients. Post-approval studies are thus no more than a marketing tool.

Consider the following witness given to the House of Commons Report on *The Influence of the Pharmaceutical Industry*, 2004-05:[65]

> In order for a drug to be licensed it has to show that it is more effective than a placebo, usually in two controlled trials. However, according to Prof Healy, companies can run 10 or more trials in carefully selected samples using instruments designed to pick up any effect and, even if the results show that the drug failed to beat placebo in the majority of trials, the drug may still be licensed. The trials producing negative results

are commonly identified as failed trials rather than drug failures. Whether the experimental drug is compared to placebo or a comparator drug will affect the outcome. Common flaws in trial design include the use of inappropriate comparator drugs, such as those associated with a higher risk of side-effects than others in the therapeutic group. Selection of dosage may also be used to skew results. Administration of a comparator drug in unduly low doses may result in reduced levels of efficacy. Administration of the comparator drug at relatively high dosages might make the test drug appear safer than it really is. These and other methods of trial design may show the new drug in a misleadingly positive light.

Also of concern, because it may lead to an over-estimate of the drug benefit, is reliance on surrogate markers of efficacy or disease (in one case, higher numbers of extra abnormal heartbeats were assumed to correlate with increased risk of death.) However, such markers may not be directly relevant to treatment outcomes (in this case, drugs used to reduce the number of heartbeats were actually associated with increased mortality.) The use of combined clinical outcomes can also be problematic; making it difficult to assess which end point has really changed, while the use of inappropriate safety markers makes extrapolation to safety in clinical practice even harder. Cancer Research UK criticised the industry for not investigating the wider effects of drugs and focusing on specific outcomes.

Several witnesses were also concerned about the duplication of research. Some organisations make considerable efforts to avoid this problem: the MRC requires groups seeking financial support to identify existing evidence before applying, to show that the new research builds on previous lines of investigation. On the other hand, others either did not attempt to find out about previous research or could not get access to it. Sir Iain Chalmers argued that a systematic review of existing evidence prior to the planning and reporting of new clinical trials should be mandatory. The following example shows what can happen if such a review is not undertaken:

> After reviewing the experience of thousands of patients who had participated in controlled trials of new calcium-blocking drugs given to people experiencing a stroke, a Dutch team found no evidence to support the increasing use of these drugs in practice, or for the large numbers of clinical trials that had been performed…Furthermore, when they subsequently prepared a systematic review of the relevant animal studies they found that these had never suggested that the drug would be useful in humans.

Disease Mongering: 'Corporate Construction of Disease'

One of the important ways drug companies make money is by telling people they are sick, even when they are passing through one of life's many normal transitions. This 'disease-mongering' suits the medical profession too, as it helps in medicalising problems. [For more on the phenomena of disease mongering, see the papers at *PLOS Medicine*, April 2006, http://collections.plos.org/diseasemongering-2006.php]

Some examples:

- In India, piracetam is being promoted for vague conditions like "intellectual decay," "social maladjustment," "lack of alertness," "changes of mood," "deterioration in behaviour" and "learning disabilities in children associated with the written word." The recommended duration of treatment for the last indication is "entire school year"

in dose of "3g per day" i.e. 7-8 capsules of 400 mg daily. If the drug is administered for the entire school year as recommended, it will mean parents buying at lease 2,700 capsules at a cost of Rs. 12,775 year after year. The unending claims of the drug's efficacy include the treatment of sickle cell anaemia, stroke and vertigo. In Britain, piracetam (Nootropil) is permitted for use in just a single indication, a rare disorder called cortical myoclonus, that too only as an adjuctive therapy (Reference: Britain National Formulary). While in India, the drug is being promoted for use in young children, in Britain its use is contraindicated for adolescents under the age of 16 years. "If the Indian company marketing piracetam is to be believed, the drug is nothing short of nectar. It has no contraindications, no need to observe any precautions, no interactions and no adverse drug reactions. In Britain, the drug is contraindicated in hepatic an renal impairment, during pregnancy and lactation. It is to be used cautiously in elderly. Its side effects include: diarrhea, weight gain, insomnia, nervousness, depression, hyperkinesias and rash. It can interact with warfarin and result in bleeding. Piracetam is not marketed in the United States."[66]

- Buclizine (brand Longifene in India) is being promoted as appetite stimulant while the drug itself is not commercially available in the US and is restricted worldwide for treatment of migraine in combination with analgesics. Internationally reported adverse effects include: drowsiness, blurred vision, diarrhea, difficulty in passing urine, dizziness, dryness of mouth, tachycardia, headache, nervousness, restlessness, hallucinations, skin rash and upset stomach. Bottles of Longifene, the only brand of buclizine being sold in India do not contain either the package insert or the patient information leaflet.[67]
- Ever since Hepatitis B vaccination started being made by Indian companies starting with Shanta Biotech of Hyderabad, the classes of people who "need" Hepatitis vaccine compulsorily has been expanding; the Ministry of Health and Family Welfare (MOHFW) would have us believe that it is a bigger problem than AIDS (so is iron deficiency anemia). And suddenly India has had a glut of Hepatitis B vaccine manufacturers – all in search of a market. Some of them were/are even on the verge of closing. They have all succeeded in convincing policy makers that hepatitis B vaccine need to be given to all newborns by including it in the National Immunization Programme. Business media have gleefully reported this as a "shot in the arm" for the ailing vaccine industry.[68]

- Warner Lambert invented a condition called "halitosis" – which makes ordinary bad smell in the breath sound serious. Sales of Listerine rose from US $100,000 to US $4 million in six years.[69]
- In the 1980s Glaxo needed to expand their market for ranitidine (brand Zantac). They again created a condition called "gastro-oesophageal reflux disease (GERD)" –which is a serious sounding name for heartburn, an age-old complaint. The company also set up a platform called the Glaxo Institute for Digestive Health, which in due course led to a PR exercise called Heartburn Across America. Annual sales of Zantac peaked at US $ 2 billion.
- "*Capturing impotence in an acronym*": During the 1990s Pfizer had to create a market for sildenafil citrate ("Viagra") and it ended up calling the broader condition of impotence as "erectile dysfunction" (ED). Calling impotence ED caused probably less embarrassment to shy patients as they could now discuss a medical problem called ED with their doctors!
- Manufacturers of fluoxetine (a serotonin re-uptake inhibitor, brand name Prozac) marketed in the name of "premenstrual dysphoric disorder," a different name for a severe form of premenstrual syndrome, a routine hormonal transition. Again here the marketing strategy was to frame the "disease prevalence to maximize the size of the medical problem." Pfizer even setup an organization called Impotence Australia that would host the advertisements in the media. In the US, Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants have been widely promoted through what is called Direct-to-Consumer Advertising (DTCA). In a paper published in *PLOS Medicine*, Jeffrey R. Lacasse, Jonathan Leo observe:[70] "The impact of the widespread promotion of the serotonin hypothesis[71] should not be underestimated. Antidepressant advertisements are ubiquitous in American media, and there is emerging evidence that these advertisements have the potential to confound the doctor–patient relationship." A recent study by Kravitz et al.[72] found that pseudopatients (actors who were trained to behave as patients) presenting with symptoms of adjustment disorder (a condition for which antidepressants are not usually prescribed) were frequently prescribed paroxetine (Paxil) by their physicians if they inquired specifically about Paxil. "In 1998, at the dawn of consumer advertising of SSRIs, Professor Emeritus of Neuroscience Elliot Valenstein summarized the scientific data by concluding, "What physicians and the public are reading about mental illness is by

no means a neutral reflection of all the information that is available."[73] The current state of affairs has only confirmed the veracity of this conclusion. The incongruence between the scientific literature and the claims made in FDA-regulated SSRI advertisements is remarkable, and possibly unparalleled."[74]

- "A legendary example of this condition (called) branding strategy was the development of Xanax (alprazolam) for panic disorder in the 1970s. In DSM-II, panic disorder fell under the broad category of anxiety neurosis. Without a well-branded condition, patients experiencing panic attacks often went to cardiologists, thinking their problem was a heart condition, only to be labeled "cardiac complainers" and hypochondriacs due to a lack of physical pathology. Dr. David Sheehan, a pioneering thought leader in the field of panic, helped characterize the condition and push for a new way to diagnose and treat it. Upjohn, the makers of Xanax, helped fund this early research, as well as publications and speaking tours to cardiologists to help raise awareness of the heart-brain connection in the minds of panic disorder patients. Xanax was the only benzodiazepine to be studied that showed clear evidence of effectiveness. Through an unrestricted grant to the National Institute of Mental Health, a three-day thought leader conference resulted in a published consensus on the diagnostic criteria of panic disorder and how best to treat it. Xanax was the first to receive an exclusive indication, thereby maintaining its leadership in anxiety disorders. Since the release of DSM-III in 1980, which first recognized panic disorder as a distinct condition, its incidence has grown 1,000-fold, and newer antidepressants."[75]
- In Australia, baldness in men was medicalised by Merck to sell its hair-growth drug finasteride (Propecia); Merck funded a new International Hair Study Institute so that men can wise up to the bald truth by consulting their doctors. Hair loss, the public was told, could lead to panic and other emotional difficulties and even have an impact on job and well-being! Needless to say there were several articles around 1998-2002 in the media about the life-threatening process called hair loss.[76]
- Irritable bowel syndrome (IBS), a common functional disorder, found a drug in GSK's Lotronex (alosetron hydrochloride) and GSK used a "medical education" firm In Vivo to "shape" medical and public opinion – a plan that included setting up an "Advisory Board", consisting of preselected KOLs (Key Opinion Leaders) in each Australian state – the campaign was stopped because the US FDA recommended

withdrawal of the drug after reports of serious and sometimes fatal adverse reactions. FDA investigators[77] discovered that the use of Lotronex could result in ischemic colitis, a potentially life threatening condition which is caused by reduced blood flow to the colon. Additionally, the drug can cause severe constipation, which can result in a ruptured bowel. As of October 2000 there had been 91 incidences of hospitalization (many more likely went unreported) in which some patients required surgery and at least five died. As a result, GlaxoSmithKline agreed to remove the drug from the market in November 2000. However, in June 2002, the USFDA, facing pressure from desperate patients, announced June 7, 2002 the approval of a supplemental New Drug Application (sNDA) that allows restricted marketing of Lotronex (alosetron hydrochloride), to treat only women with severe diarrhea-predominant irritable bowel syndrome (IBS).

- In 1997, Roche started promoting its antidepressant Aurorix (moclobemide) as a valuable treatment for "social phobia" – its PR company issued a press release saying more than one million Australians had a "soul-destroying condition" called social phobia. Soon Roche's promotion of Aurorix became case-study material of positive action in marketing circles even as the medicalisation of human misery was pushed further.

Drug Industry's Ghost Writers

One could understand if marketing was confined to inventing unwarranted uses of medicines: It could be blamed on pin-striped MBAs. But we have seen research trials are illegally conducted in India with poor regulatory oversight, and it is difficult to know who is doing what clinical trial at any given time. A further and more blatantly unethical form of manufacturing 'consent' is by ghost writing research papers. Richard Smith, editor of the *British Journal of Medicine*, admitted ghost writing was a 'very big problem'. "We are being hoodwinked by the drug companies. The articles come in with doctors' names on them and we often find some of them have little or no idea about what they have written," he said. "When we find out, we reject the paper, but it is very difficult. In a sense, we have brought it on ourselves by insisting that any involvement by a drug company should be made explicit. They have just found ways to get round this and go undercover."[78]

> Estimates suggest that almost half of all articles published in journals are by ghostwriters. While doctors who have put their names to the papers can be paid handsomely for

'lending' their reputations, the ghostwriters remain hidden. They, and the involvement of the pharmaceutical firms, are rarely revealed.

These papers endorsing certain drugs are paraded in front of GPs as independent research to persuade them to prescribe the drugs.

In February the *New England Journal of Medicine* was forced to retract an article published last year by doctors from Imperial College in London and the National Heart Institute on treating a type of heart problem. It emerged that several of the listed authors had little or nothing to do with the research. The deception was revealed only when German cardiologist Dr Hubert Seggewiss, one of the eight listed authors, called the editor of the journal to say he had never seen any version of the paper.

An article published last February in the *Journal of Alimentary Pharmacology*, which specialises in stomach disorders, involved a medical writer working for drug giant AstraZeneca - a fact that was not revealed by the author.

The article, by a German doctor, acknowledged the 'contribution' of Dr Madeline Frame, but did not admit that she was a senior medical writer for AstraZeneca. The article essentially supported the use of a drug called Omeprazole - which is manufactured by AstraZeneca - for gastric ulcers, despite suggestions that it gave rise to more adverse reactions than similar drugs.

Alexei Koudinov, MD, PhD, neuroscientist and an editor, in response to a *BMJ* paper[79] on the uneasy relationship between medical journals and pharmaceutical companies responded in a letter:[80]

> …Last week I and my colleagues were digesting May 22, 2003 *Neuron* (a major neursocience journal published by Cell press) article and associated editorial coverage[81] on a validity of the Alzheimer's amyloid-based therapy (read 'amyloid cascade hypothesis'.)
> I and others found that the title and some of the conclusions of this study are not yet justified. Moreover, the authors provided apparently false statement that “they have no competing financial interests related to Elan/Wyeth-Ayerst,” a vaccine maker, creating a rationale to consider the article "a bias in favor of the expired amyloid dogma-based Alzheimer’s therapy approach."
> This week’s *BMJ* editorial is confident that "journals are caught between publishing the most relevant and valid research and being used as vehicles for drug company propaganda." In light of the above I wonder to which category the latest *Neuron* articles on Alzheimer's disease belong to.
> I believe that many neuroscientists are puzzled, too, especially because similar question was earlier discussed (see below message to remember) for the consensus recommendations for the post-mortem diagnosis of Alzheimer's disease by the NIH National Institute on Aging a key citation of the *Neuron* study…. (*citations in the original letter)*

Box 8: Alzheimer's Disease Research: A Message to Remember

Science, and biomedical science in particular, is competitive, and for many is a pursuit that generates considerable passion and emotion. No wonder, then, that competing scientists working in the most competitive disciplines occasionally come to blows.

Research into... Alzheimer's disease seems to suffer more than most in this respect. Judging by recent events, this reputation seems justified...

Source: Nature *Medicine*, July 1999 5(7):713, 717

Another more revealing response was from a former ghostwriter, Susanna Rees (see Box 7 *Who Actually Wrote the Research Paper*).

Box 9: Who Actually Wrote the Research Paper? How to Find it Out?

In reply to the *BMJ* theme issue of May 31, 2003 (Vol 326 issue 7400) 'Time to untangle doctors from drug companies'[82]

Until the end of 2002, I worked for a medical writing agency as an editorial assistant. I believe that the agency I worked for generally has standards of practice that are consistent with best practice within the industry. I write to you about the broader issues associated with general practices in the industry.

It is my perception that there is consistently a high turnover in staff throughout all branches of the pharmaceutical industry. It is also my perception that the effect of this is that there is often a lack of consistent follow-through on how the pharmaceutical industry acquires data, monitors it, processes it, validates it.

Medical writing agencies go to great lengths to disguise the fact that the papers and conference abstracts that they ghost-write and submit to journals and conferences are ghost-written on behalf of pharmaceutical companies and not by the named authors. There is a relatively high success rate for ghost-written submissions - not outstanding, but consistent.

One standard operating procedure I have used states that before a paper is submitted to a journal electronically or on disk, the editorial assistant must open the File Properties of the Word document manuscript and remove the names of the medical writing agency or agency ghost-writer or pharmaceutical drug company, and replace these with the name and institution of the person who has been invited by the pharmaceutical drug company (or by the agency acting on its behalf) to be named as lead author, but who may have had no actual input into the paper.

Quality-assurance auditors vet the standard operating procedures of the agency I worked for. I am surprised that these auditors, presumably following government guidelines, do validate such a procedure, which is actually in place in order disguise the true authorship from the editorial boards of journals. This area seems very blurred. This practice is contrary to the principles of openness and transparency of the scientific method.

The full file history of every Word document may be retrieved, using a Texteditor or a Hexeditor. It is impossible to change that history or to disguise who actually created the Word document or the name of the organisation of origin. Office applications can reveal the full chronology of authors, file paths, file names, file amendments, and details of the computers used. Text, graphics or tables that have been inserted into a Word file will contain the full history of the document that they were extracted from. Technical effort is required to identify this information [1,2]. Such a check might be made prior to peer-review, using an original file, saved onto disk by the authors and included as part of the submission package to the journal. Even this check may not be exhaustive or conclusive: for example, where a file has been exported into .RTF format, much of the original file history may be lost. A Word document that has been exported into

.RTF format and subsequently back into .DOC format, may possibly lose much of its original Word file history. RTF offers a "track changes" option, so it may be possible to view the entire text-editing history of a Word document that has been exported into .RTF format. A file that has been exported into .PDF format will have lost its entire history.

On-line submission of ghost-written papers and abstracts to journals and conferences is done from the agency computer or sometimes from the offices of the pharmaceutical company. Do journals and conference organisers always try to identify the organisation that actually submitted the electronic file?

An internet engine search on the authors of a paper will quickly reveal whether these names are closely linked to pharmaceutical drug companies, to their products or publicity materials.

The interests of the pharmaceutical industry lie at the heart of many current, urgent debates: GM food, anti-depressants and their side-effects, and others. We need to ask: Who wrote this paper? Who did this research? Are the objectives of this research genuinely impartial? Is this process fully transparent?

Independent authorship and impartiality are the cornerstones of scientific research. The pharmaceutical giants are using the tools of scientific research as a marketing tool. I believe that these marketing practices are damaging the authority and effectiveness of pharmaceutical research. With thanks to Doro Mücke-Herzberg

References

(1) PC-Welt (German language publication) 1999(7): 242-243. "Verborgene Infos" (trans: Hidden information) Springer T, Apfelböck H. (2) c't (German language publication) 2002(3): 172-175. "Dokumente durchleuchtet: Was Office-Dateien verraten können" (trans: Documents under the X-ray: what Office files can tell you) Rost M, Wallisch A.

Competing interests: None declared
Source: Susanna T Rees, Care Assistant, BMJ*, 12 June 2003. Citations in the original at <http://bmj.bmjjournals.com/cgi/eletters/326/7400/1202#33226>*

Other Real Problems

"It is very surprising," say Chauhan, Rani and Padh that "to be approved by the Food & Drug Administration (FDA), it has to show efficacy only in one third of the population. It is very much likely that this one third population may belong to one particular group showing good effect of the medication, but the same drug, even after being approved by the FDA may have adverse or less effect or even may not have effect at all in rest of the two third populations. Some very well known examples of such cases are shown in the Table 2.

Table 2: Examples of Poor/Non-Responders to Various Therapies

Disease	Therapy	% of non-responders
Various cancers	Various	70-100%
Asthma	Beta-2 agonists	40-75%
Diabetes	Sulfonylureas	25-50 %
Depression	Tricyclics,	20-40 %,
	Selective Serotonin-Reuptake Inhibitors (SRRIs)	25-50 %
Duodenal Ulcer	Proton pump inhibitors	20-90 %
Hypertension	Thiazides	50-75 %
	Beta-blockers	20-30 %
	ACE inhibitors	10-30 %
	Angiotensin I antagonists	10-30 %
Osteo/rheumatoid Arthritis	Nonsteroidal Anti-Inflammatory Drugs (NSAID), Cyclooxygenase-2 (COX-2) inhibitors	20-50 %

*Silber, B.M., Kalow, W. and Meyer, U., Eds., in *Pharmacogenomics*, Marcel Dekker publishers, New York, 2000. Quoted in: Neelam Chauhan, Shubha Rani, Harish Padh "Pharmacogenetics: Genetic Basis for Rational Drug Therapy."

V

Barrier Building: Technical and Commercial

A great deal of knowledge construction and illegitimation occurs motivated by the need to ward off competition by barrier building (no free market this) intermingled with atavistic impulses of neo-colonialistic impulses and reverse protectionism from advocates of globalisation and global level playing fields. We consider two issues: the discourse on intellectual property and the construction of counterfeitness. .

Invention, Discovery and Patents

One of the more contested routes of knowledge legitimation as much as knowledge production, with direct implications for human welfare is the area of intellectual property.

Countries and companies having arrived at a stage of development, chose to put up the gates for others in the race. "The natives … always arrive late at the destination," trying to fulfill someone else's conception of the healthy life.[83] Most of us having fallen for the lures of modern medicine, and modern science, have but no option but to battle this barrier building, and to one's regret almost exclusively within the confines of the modern medicine paradigm of white coats, aseptic labs, and now genomes. It is here we are told despite the Newtonian proclamation of seeing-further-because-of-standing-on-the-shoulders-of-giants that for certain forms of inquiry in disease prevention, one needs to look over one's shoulders as contrasted to standing on those of others, as to what laws of property and theft prevention are we violating.

If patents promote innovation, how were the great epiphanic discoveries in 20th century science and technology made without such a reward system? How indeed did the great mass of Indian populations across the centuries survive without patents? Indeed

> ...if patents were the source of medical innovation as claimed by intellectual monopoly apologists, the large historical and cross country variations in the patent protection of medical products should have had a dramatic impact on the pharmaceutical industries of the different countries. In particular, at least between 1850 and 1980, most drugs and medical products should have been invented and produced in the United States and the United Kingdom, and very little if anything in continental Europe. Further, countries such as Italy, Switzerland and, to a lesser extent, Germany, should have been the poor sick laggards of the pharmaceutical industry until the other day. Instead, as everyone knows since high school, the big time opposite is and has been true. This is as macroscopic a contradiction of the intellectual monopoly apologists' argument for patents in general, and for medical patents in particular, as one can possibly imagine.[84]

The first round in this battle has been won by those wanting tighter IP laws – the April 2005 amendments to the Indian patent laws and TRIPS/WTO have ensured that.

But what are being now demanded are other privileges which go by the name of data exclusivity and data protection. "Data exclusivity" is a provision that would preclude for a period of years both generic manufacturers and the regulatory authorities (in India, the Drug Controller General of India) from relying on clinical trial data submitted by an originator company to prove the safety and efficacy of the drug. Data exclusivity guarantees additional market protection for originator pharmaceuticals by preventing health authorities from accepting applications for generic medicines during the period of exclusivity. India's amended patent provisions are silent on data exclusivity.

Indeed the April 2005 amendments to the Indian Patents Act have now restricted the scope for the granting of Patents on frivolous claims. 'Inventive step', 'novelty' and 'product' were less clearly defined earlier leading to fear of evergreening of patents – evergreening is finding new uses for drugs whose patents are on the verge of expiry and demanding the new uses be patentable. Normatively, the definition of invention should be restricted to basic novel invention with all escape routes to evergreening closed. The Act now clarifies that an 'inventive step' means a feature of an invention that "involves technical advances as compared to the existing knowledge or having economic significance or both." The amended Act contains a new definition for "new invention" by stating that it means "any invention or technology which has not been anticipated by publication in any document or used in the country or elsewhere in the world before the date of filing of patent application with complete specification, i.e. the subject matter has not fallen in public domain or that it does not form part of the state of art." The amendments also provide a definition for "pharmaceutical substance" as being "a new entity involving one or more inventive steps".

To minimize evergreening, the amended Indian Patents Act Section 3d clarifies that "the mere discovery of a new form of a know substance which does not result in the enhancement of the known efficacy" is not patentable. It further explains that: "Salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substances shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy."

Even as we write this, white coats with the help of black coats are contesting[85] every line of the patent law including the definition of 'efficacy', a new chemical/molecular entity and the difference between 'incremental modification' and 'innovation'. Helped in no small measure by the pronouncements of a Government Committee headed by one of India's scientist czars, Ramesh Mashelkar. According to the Mashelkar Committee,[86] Section 3d referred to above is not TRIPS compliant. That is it would not be TRIPS compliant to limit granting of patents for pharmaceutical substance to New Chemical Entities only. But the Mashelkar Committee goes on with classic on the one hand/other hand casuistry: "However, every effort must be made to provide drugs at affordable

prices to the people of India. Further, every effort should be made to prevent the grant of frivolous patents and 'ever-greening'. Detailed Guidelines should be formulated and rigorously used by the Indian Patent Office for examining the patent applications in the pharmaceutical sector so that the remotest possibility of granting frivolous patents is eliminated." The Committee also concluded in its wisdom: "Excluding micro-organisms *per se* from patent protection would be violative of TRIPS Agreement."

Both these recommendations could have come from the mouth of the big pharma lobby horse and it appears in fact it did.[87] If implemented as law it would knock the bottom of some hard won provisions of the amended Patents Act 2005. But the point is for a committee of such eminence there is no socio-historical examination of what constitutes a new chemical/molecular entity or the fact that the disjunct between a naturally occurring microorganism and an artificially engineered one is not so clear cut as claimed even as there is a continuum between Kepler's laws and Newton's Law of Gravitation.

Patents provide the means for drugs to become private property and monopoly. Data exclusivity/data protections, evergreening, are means to extend this monopoly by regulating even downstream use by consumers and other knowledge workers and researchers. A Newton would think twice before standing in public on anybody's shoulders.

Counterfeit Drugs: Construction of Terms of Discourse

What is a counterfeit drug? A counterfeit drug is defined differently in different countries. In order to address this problem the following definition has been developed by the World Health Organization:

"A counterfeit medicine is one which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging."

The problem of counterfeit drugs is known to exist in both developed and developing countries. However, the true extent of the problem is not really known since no global study has been carried out.[88]

The drugs counterfeited could include antibiotics, hormones, analgesics, steroids, and antihistamines. Counterfeit products can be grouped into at least six categories:

- Products without active ingredients
- Products with incorrect quantities of active ingredients
- Products with wrong ingredients
- Products with correct quantities of active ingredients but with fake packaging
- Copies of an original product
- Products with high levels of impurities and contaminants

Suffice it to say we need to distinguish the terms used in normal discourse, often interchangeably: terms like 'counterfeit', 'fake', 'substandard' drugs and 'poor quality' drugs. And drugs, which are copied without approval from the patent holder. Current laws in India prohibit counterfeit drugs in all the senses above. In some countries the issue is more complex and there is no distinction made between counterfeit and substandard drugs.

In developing countries a wide spectrum of types of counterfeit drugs, ranging from the precise copy of a genuine product to the extreme case of a drug product with none of the correct active ingredient exist. Some include as counterfeit even unregistered drugs imported in the country – for other than personal use. Consequently, counterfeit drug is defined broadly in order to cover drug products that have been copied or forged as well as certain substandard products, particularly those intentionally made to be substandard.[89]

In a response to allegations by Harvey Bale, the Director General of the International Federation of Pharmaceutical Manufacturers Association (IFPMA), of copying and counterfeiting by India and Brazil, economist Bibek Debroy in a column in *Financial Express* pointed out[90]:

> … There is a difference between copying and counterfeiting. Copying is when you steal someone else's intellectual property and pass it off as your own. Counterfeiting is faking. You produce a product (incorporating intellectual property) that pretends to be someone else's. Your product is passed off as someone else's brand. Unfortunately, the word piracy is used for both copying and counterfeiting and this sometimes causes confusion...
>
> …The (Indian) law may permit some varieties of copying. But counterfeiting is prohibited. In every country, including India … there are around 20,000 pharmaceutical producers in India. With such a large, fragmented and heterogeneous industry, it is impossible to generalise. There are large (Indian) companies that are taking on the world (which is perhaps the reason IFPMA is upset) and there are producers who operate out of

> garages. Of course, there are sub-standard drugs in the market. Standards don't exist, or are hopelessly out of date, or are not enforced. Of course, there is copying. Of course, there are counterfeit drugs. But that's not what IFPMA is saying. IFPMA is tarring the entire Indian pharmaceutical industry with the same brush.
>
> Take quality and assume for the moment that quality standards are non-existent in India. But the Indian pharmaceutical industry also exports. The present battle in the World Trade Organisation is primarily about African countries importing certain drugs from countries like India and Brazil. India does export to Africa. However, India also exports drugs (and not just bulk drugs or drug intermediates) to the US as well and these have to comply with FDA (Food and Drug Administration) norms. I have been told, and IFPMA will correct me if I am wrong, that FDA norms are fairly stringent and not sub-standard. If that is true, it logically follows that the entire Indian pharmaceutical industry doesn't produce poor quality drugs. If American law is tough about counterfeiting, and the law is enforced, these exported drugs can't be counterfeit either. And since some Indian pharma companies have obtained patents in the US, these can't be the result of copying.
>
> …. India has strengths in intellectual property, including pharmaceuticals. India doesn't need to copy. Counterfeiting has to stop and not because IFPMA thinks it should. …However, there is genuine concern about public health issues in several African countries. In the entire AIDS debate, the international pharmaceutical industry made a hash of public relations. If the IFPMA letter is any indication, industry hasn't learnt from that PR disaster.

Also what does one call the rush of me-too drugs put out by world pharma leaders, the drugs on which inadequate research is done, especially on effects of drugs marketed in children, old persons and women, and drugs for which new uses are found just to extend its patent period? Consider for instance what Dr Richard Nicholson, editor of the *Bulletin of Medical Ethics*, told the House of Commons Health Committee:

> A clinical trial was proposed to my ethics committee some years ago of Vioxx versus naproxen and we wondered to ourselves why on earth Merck want to compare this with naproxen. They did not give us the details initially and then when we asked and asked, we finally found out that they had already carried out major trials against the two major anti-inflammatory drugs…and found absolutely no advantage of their drug. They were hoping that by comparing it to naproxen, which had just five per cent of the market, they would be able to show an advantage. [91]

Counterfeit? In that case many of the leading Pharma companies in the world would stand accused of pushing counterfeit drugs.[92]

VI
Comments

Reviewing the discourse traversed in this chapter we find the following:

- Irrationality in production, prescription and use of medicines.

- Lack of application of mind in regulation and licensing which in the first place leads to the prevalence of irrationality.[93]
- The free market works myth in pharma and health services leading to anomalies in drug pricing; and specifically overpriced and inaccessible drugs.
- Asymmetry of information in the pharma market and therefore no meaningful choice for the endusers adding to lack of access.
- The disjunct between the left and right hand of the government leading to ignoring useful recommendations that are inconvenient to previously held beliefs. We saw this also in the nimesulide case where a opinion poll of 50 Delhi doctors was used to settle the issue.
- The construction of the 'counterfeitness' of medicines accompanied by attempts to harmonise, a kind of civilising-the-savages by ushering poor folks into modernity.[94]
- Disease-mongering, construction of ailments for drugs in search of a cure, clinical trials with ethical and intellectual problems papered over (literally in a sense too), the doubtful authenticity and veracity of research and constructed knowledge reported in medical journals, the underplaying of conflicts of interests, the problematic enunciation of what constitutes a cure, etc.
- The above when sought to be extrapolated to larger spaces feeds into the pretence of certainty of knowledge[95] in public health policy making leading to unfortunate consequences, of which the muddle over pulse polio vaccination is just one instance.

Across then a wide spectrum, the following processes seem to distort the cultivation and development of knowledge/expert skills in the pharma industry and its markets, in the medical profession and its collegiums, and in public health policy making and among its gatekeepers and minders.

1) Drug companies, and most medical professionals who get persuaded by them, would probably be most happy if much more of our lives were medicalised. Scientific objectivity in medicine, at the best of times a contested term, seems to be a compromised idea in medicine and its practice. The game of science is played by shifting goal posts which is okay if it is followed by genuine paradigm

shifts in reading of reality. However pharma companies and the commercial interests behind them have a dominant role in shifting these goal posts and defining the benchmarks in medicine. Safety, rationality and reason seem to be ignored at will and defined/redefined at best by the dictates of the bottom line, and at worst idiosyncratically.

2) Unfortunately medical professional associations and regulatory authorities give the impression of willingly bending to the logic of big pharma.
3) When pharma gets embedded in public policy space, the collective welfare of humanity, and the poorest among them, is given a go by in public health policy making. Indeed public health policy making gives the feeling of illogical decisions, of no mind behind the issues at stake, namely disease and its cure among large populations. Decision making, at least in the examples we have quoted, seems to be a way for justifying one's beliefs and prevalent fashions.
4) The incidence of much disease of a certain kind gets decreased with increasing and better access to clean water, sanitation, food, hygiene, social security, equity and education that is convivial. Neither big pharma nor dominant segments of the medical profession and bureaucracy want such "social agendas" to overwhelm the game of markets-magic-medical bullets-technocratic-fixes.
5) What can one say of the character of accumulated experience in such circumstances – experience that variously goes as knowledge, expertise and wisdom? We submit that such knowledge is distorted having been built on false premises and a significant chunk of the received wisdom therein at best contentious if not altogether spurious: evidence biased than evidence based.
6) The Hippocratic exhortation - "do no harm" - is violated quite so often as to become passé in regular medical practice. In fact deviations from the deviant practice of medicine is viewed as violation of the Hippocratic oath, if you just hear the talk among medical practitioners in India who are also successful capitalists of clinical practice. Therefore it may be better to ask the question what is the more ethical way to practice medicine in a society like that obtaining in India where the majority is pauperised beyond repair.
7) The predominant form of medical expertise is a valorised term for the sophistic blindness which medical experience develops into. Like the Glass Bead game of Thomas Mann, it is a game, a way of structuring time for the practitioners with

meaninglessness and hopelessness writ on it for the majority on whom it is practiced, gaping into from outside the gated communities and barbed wire fences. Concerns like intellectual integrity, bioethics and compassion and care remain as intrusions leading at best to unclarifications[96] for those who define the benchmarks and goal posts. Such expertise and knowledge legitimation processes are harmful for our collective long-term health, dangerous; and indeed invalid even as attempts continue to be made to legitimise and sacralise it through rent-collecting devices like intellectual property rights and through mythology like invisible hands leavening the bread into equal portions.

Another fundamental issue is that of what constitutes the 'real' truth in medicine? This arises from the theme of this chapter: knowledge legitimation - in the practice of medicine as a body of knowledge and the advocated use of medicines in therapy and cure. Legitimation implies there is something illegit with the prevailing dominant paradigm(s) and epistemic(s). Which is certainly the case if one looks at the prevalence of irrational therapy, the legitimation of it by popular practice of influential practitioners (the Delhi IMA?) and influential expert bodies (the IAP?). Indeed it is a statistical wonder how despite such low chances of rational therapy, of rational treatment and of compliance by patients in Indian settings of asymmetry of knowledge and purchasing power, patients happen to get well – it does seem to suggest that the very act of participation in the clinical process of consultation and diagnosis enhances the body's healing processes, thanks also to the natural course of disease process and probably the placebo effect and some version of the Hawthorne effect. Sometimes, it works the other way too, for worse that is, in many cases: we do not know about how worse because of poor adverse drug reaction reporting processes and poor reportage, but for anecdotal reports, of non-response to standard therapies. What we do know for certain is that there is increasing resistance to antimicrobials and especially in TB in India multidrug resistance is a looming problem, with first line and second line drugs proving useless. Both the misuse, and misprescription, of antimicrobials by prescribers and poor compliance has exacerbated the problem.

At the best of times, with relatively unbiased clinical trials, interpretation of what constitutes a good clinical trial study, efficacy and effectiveness of treatment are

contested issues. Among many such issues, the question of informed consent exhibits particular poignancy when you realise that emotive public health programmes like mass polio campaigns have their knowledge base built on shifting sands. Informed consent is much bandied about but is informed consent taken across populations when such contested policies are made the norm? What information can you give as a healer - represented here by the State – and obtain consent thereon, when the socially and legally sanctioned expert does not have information as to its efficacy, side-effects and potential for long-term damage?

Is there then a Truth (with a capital T) in medicine? Are there truths, as in valid statements with limited validity, in medicine? Do we in post-modernistic wilfulness declare that all truth in medicine is socially and culturally mediated? Admittedly, after Foucault, notions of power mediate ideas about truth and what constitutes the "evidence" in evidence-based medicine. In addition, our reading of reality and making sense of sensory data is theory laden,[97] and one may add ideology/class/caste/gender laden. As one consequence what is truth is defined, not wholly though and thankfully so, by: standard practice (which in itself may be irrational in certain epistemic domains) as seen by repeated application of certain rules and procedures in treatment; by the construction of diseases to suit certain chemicals developed with an eye on the market for illness and health; the idea of what constitutes cure, efficacy, safety and validity; the notion of what constitutes an acceptable adverse reaction and side-effect;[98] the influence of pharma companies on clinical trials and what results get published (why is there a predominance of positive reportage of "successful" clinical trials?); and therefore what gets into the medical textbooks and reproduced across generations.

This much can be somewhat accepted as given, though not palatable, that the political economy of the pharma industry defines truth significantly, if not substantially and wholly, in medicine as much as does dominant medical practice. In fact the political economy of 'truths' in medicine somewhat parallels the dominant political economy of our times even as it works the other way too. [This happens routinely in the construction of the 'good' doctor, the 'good' hospital, 'affordable' health care, the idea of "excellence" in quality of care and "important and useful " research in pharma, etc.]

However what needs to cause alarm bells is that this mediated wisdom of medicine is purveyed across populations as signified by public health policies affecting millions: the fiat of an almost compulsory vaccination schema, or a doubtful provider-controlled contraceptive, or a sheer denial of a recourse to overcome an iron-deficiency anemia by elementary lack of availability of iron-folic acid tablets because it is too affordable for the patient!. Not only medicines but public health and pharma policies have adverse reactions and side-effects. Common people's bodies are used to do research upon, but access to actual data submitted in the clinical trials and drug regulatory process are shrouded in secrecy.

As sophisticated a defendant of the market as Hayek had this to say in his Nobel Lecture, *Pretence of Knowledge:*

> It is indeed the source of the superiority of the market order, and the reason why, when it is not suppressed by the powers of government, it regularly displaces other types of order, that in the resulting allocation of resources more of the knowledge of particular facts will be utilized which exists only dispersed among uncounted persons, than any one person can possess. But because we, the observing scientists, can thus never know all the determinants of such an order, and in consequence also cannot know at which particular structure of prices and wages demand would everywhere equal supply, we also cannot measure the deviations from that order; nor can we statistically test our theory that it is the deviations from that "equilibrium" system of prices and wages which make it impossible to sell some of the products and services at the prices at which they are offered.[99]

He could have been speaking of the pretence of certainty and knowledge in certain segments of medicine as practised today.

What constitutes valid knowledge in contemporary medicine, and as a derivative, valid public health policy making, has to be taken with a pinch of salt - if the examples and case studies cited are anything to go by. One needs to develop expertise to discern when the bathtub and bath water needs to be discarded. The time has also come to recognise that some of the emperors and gate keepers have ill-fitting or no clothes.

To use a cricketing metaphor, we need to get the match-fixers and brokers out of the way.

Annexure 1

Conflict of Interest: My Journey

These are some of the 34 slides in a power point by the former Editor of *BMJ*. Ppt at < www.bmj.com/talks>, accessed Nov 15, 2005.

Richard Smith, former Editor, *BMJ*

How Common are Competing Interests?

- A quarter of US researchers have received pharmaceutical funding
- Half have received "research related gifts"
- An analysis of 789 articles from major medical journals found that a third of the lead authors had financial interests in their research—patents, shares, or payments for being on advisory boards or working as a director.

Bekelman JE, Li Y, Gross CP. "Scope and impact of financial conflicts of interest in biomedical research. A systematic review." *JAMA* 2003; 289: 454-65.

How Common are Competing Interests?

- 75 pieces giving views on calcium channel blockers
- 89 authors
- 69 (80%) responded
- 45 (63%) had financial conflicts of interest
- Only 2 of 70 articles disclosed the conflicts of interest.

Stelfox HT, Chua G, O'Rourke K, Detsky AS. "Conflict of interest in the debate over calcium channel antagonists." *N Engl J Med* 1998; 338: 101-105.

Do Authors Declare Conflicts of Interests?

- 3642 articles in the five leading general medical journals (*Annals of Internal Medicine, BMJ, Lancet, JAMA,* and the *New England Journal of Medicine*)
- Only 52 (1.4%) declared authors' conflicts of interest

Hussain A, Smith R. "Declaring financial competing interests: survey of five general medical journals." *BMJ* 2001; 323:263-4.

Does Conflict of Interest Matter?

- 11 studies compared the outcome of studies sponsored by industry and those not so sponsored
- In every study those that were sponsored were more likely to have a finding favourable to industry
- When the results were pooled the sponsored studies were almost four times more likely to find results favourable to industry.

Bekelman JE, Li Y, Gross CP. "Scope and impact of financial conflicts of interest in biomedical research. A systematic review." *JAMA* 2003; 289: 454-65.

Does Conflict of Interest Matter?

- 106 reviews, with 37% concluding that passive smoking was not harmful and the rest that it was.
- Multiple regression analysis controlling for article quality, peer review status, article topic, and year of publication found that the only factor associated with the review's conclusion was whether the author was affiliated with the tobacco industry.
- Only 23% of reviews disclosed the sources of funding for research.

Barnes DE, Bero LA. Why review articles on the health effects of passive smoking reach different conclusions. *JAMA* 1998; 279: 1566-1570

Does Conflict of Interest Matter? Third Generation Contraceptive Pills

- At the end of 1998 three major studies without sponsoring from the industry found a higher risk of venous thrombosis for third generation contraceptives; three sponsored studies did not.
- To date, of nine studies without sponsoring, one study found no difference and the other eight found relative risks from 1.5 to 4.0 (summary relative risk 2.4); four sponsored studies found relative risks between 0.8 and 1.5 (summary relative risk 1.1)
- The sponsored study with a relative risk of 1.5 has been reanalysed several times, yielding lower relative risks; after this failed to convince, a new reanalysis was sponsored by another company.
- One sponsored study finding an increased risk has not been published.

Vandenbroucke JP, Helmerhorst FM, Frits R Rosendaal FR. Competing interests and controversy about third generation oral contraceptives. *BMJ* 2000; 320: 381.

Sponsored Research

- A systematic review found 30 studies that compared research funded by drug companies research funded by other sources
- Company sponsored research more likely to be published
- Studies sponsored by pharmaceutical companies were more likely to have outcomes favouring the sponsor than were studies with other sponsors (odds ratio 4.05; 95% confidence interval 2.98 to 5.51; 18 comparisons)
- None of the 13 studies that analysed methods reported that studies funded by industry was of poorer quality

Joel Lexchin, Lisa A Bero, Benjamin Djulbegovic, and Otavio Clark Pharmaceutical industry sponsorship and research outcome and quality: systematic review
BMJ, May 2003; 326: 1167 - 1170.

What proportion of trials in the five major general journals are funded by industry?
75% in *Annals of Internal Medicine, Lancet, JA*MA, and *NEJM*
30% in *BMJ*

***Nature Neuroscience* and Conflict of Interest**

- Charles Nemeroff, professor of neuropsychopharmacology at Emory University School of Medicine, Atlanta, published a review on mood disorders in the February issue of *Nature Neurosciences*
- Declared no conflicts of interest.
- Dermal lithium patch that the review mentioned favourably
- Member of the scientific advisory board of Corcept Therapeutics—a company carrying out trials with mifepristone, which was mentioned favourably in the review—and, as such, was given an option to purchase 72 000 shares at a total cost of $21.60.
- Director and chairman of the psychopharmacology advisory board of Cypress Bioscience, which has only one product—milnacipran—which was mentioned in the review.

Notes

[1] This essay is for a forthcoming book. Parts of this essay, specifically parts of Section 1 and 2, have been published by the author in *Economic and Political Weekly,* Dec 16, 2007 co-authored with Anurag Bhargava; and in *A Lay Person's Guide to Medicines: What is in them and what is behind them*, LOCOST, Vadodara, 2006. Some extracts from the latter have also been co-authored with Anurag Bhargava. Parts of Section 4 and 5 are also from *A Lay Person's Guide to Medicines*. Arguments, but not the interpretation, in Section 3 is paraphrased from works attributed to Anant Phadke/JSA (see below). The author alone is responsible for interpretations, errors and omissions.

[2] "According to a study conducted by MSF, 67 per cent of the medicines produced in India are exported to developing countries; approximately 50 per cent of the medicines distributed by the United Nations Children's Fund in developing countries come from India; in Zimbabwe, 75 per cent of the tenders for medicines for all public sector health facilities come from Indian manufacturers; the state procurement

agency of Lesotho, the National Drug Supply Organisation, states that it buys nearly 95 per cent of all antiretrovirals (ARVs) from India. Even countries that manufacture their own medicines rely on imports of active pharmaceutical ingredients from India." Quoted in Sarah Hiddleston, "Patent trouble", *Frontline,* Volume 24 - Issue 03: Feb. 10-23, 2007.

[3] Dr Appaji, Director, NPPA, at a WHO-SEARO workshop on "Medicines in SEA Region", Chennai, Dec 22, 2003. Although NPPA monitors only 8000 brands in 20,000 packs, the actual number of brands in the market would be higher. Even if we assume that on an average each of the 4534 formulators produce only 5 brands, the total number of brands would be about 20,000. Many of the big companies have over 50 brands at a time.

[4] The formulations, but for the first four, that follow are from a July 2006 press release of All-India Drug Action (AIDAN), of which the authors are members. For more detailed analysis and arguments see *Impoverishing the Poor: Pharmaceuticals and Drug Pricing in India,* LOCOST/JSS, Vadodara/Bilaspur, Dec 2004; and *A Lay Person's Guide to Medicines*, op.cit. Section 1.1 and 1.2 were first published in, as part of, S.Srinivasan and Anurag Bhargava, "Why is Paswan's Price Reduction a Let-down?" *EPW*, Dec 16, 2006.

[5] The API or bulk drugs market is a better example of many players reducing prices – however even oligopoly like in the vital anti-TB segment of rifampicin and ethambutol has led to market failure. For more discussion on market failure in the pharma market in India, see *Impoverishing the Poor: Pharmaceuticals and Drug Pricing in India,* op.cit.

Competition to an economist means: 1.Existence of very large number of buyers and sellers, each consuming and producing a small fraction of the goods in the market. 2. The producers and consumers are such a small fraction of the market that whether they buy or sell, it has no influence over supply and demand. 3.All the items in the market must be identical. 4. There can be no substantial barriers (obstacles) to entry into, or exit from, the market. All these above exist, for the pharmaceutical sector in India. Still we have a situation where prices defy competition. With the help of branding, and sometimes without branding, pharma companies tend to resort to product differentiation. That is their aspirin is somehow better than the other aspirin. Adequate competition, and certainly, perfect competition, does not, apparently, exist in the Indian pharma market.

[6] The same drug in the same strength manufactured by two trusted companies can vary from 2 times to 20 times in their prices, which has no credible explanation other than overpricing. Levofloxacin used in infections is sold by Cipla is 7 rupees per tablet, while Aventis sells it at Rs. 95 per tablet. What is worse is that costlier drugs most often sell more because of more aggressive promotion. Hence the next statement: brand leader is also the price leader.

[7] See for instance: Srinivasan, S. 'How Many Aspirins to the Rupee? Runaway Drug Prices', *Economic and Political Weekly*, February 27-March 5, 1999.

[8] In economic literature, market failure is said to occur when inter alia: When adequate competition does not exist. Buyers and sellers are not well informed. Without information uneducated decisions are made. Resources are not free to move from one industry to another (resource immobility). Prices do not reasonably reflect the costs of production. Presence of : Negative externality- harmful side effect that affects an uninvolved third party. In most events, it constitutes external cost. In this case, production of irrational and unscientific medicines. Or 20-year long patents restricting entry of other players. Or use of unethical marketing techniques. Positive externality- beneficial side effect that affects an uninvolved third party.

1) Production of public goods (supplementation by the government or subsidy).

[9] "As a result of the costs of a single hospitalization, 35% of people fall below the poverty line. Out-of-pocket medical costs alone may push 2.2% of the population below the poverty line in one year." *(India - Raising the Sights: Better Health Systems for India's Po*or, World Bank May 2001).

[10]Recommendations/Observations of the Committee, Para 10, in *Availability and Price Management of Drugs and Pharmaceuticals.* Seventh Report, Standing Committee on Chemicals & Fertilizers, 2005-06, Fourteenth Lok Sabha, Lok Sabha Secretariat, New Delhi, September 2005.

[11] Regulation is the politically correct word of the times, an euphemism at worst and in the eyes of the industry it subsumes hopes for some kind of wishy-washy hands off price "monitoring "– never mind nobody is clear how this will be done considering promises of good behaviour of the pharma industry have never seen the light of the day.
[12] Actually the Supreme Court stayed only that part of the 2002 Policy that had to with price regulation.
[13] Five doses of Rabipur (Hoechst) with each dose costing Rs. 309.
[14] To be fair to the MOCF which drafted the policy (Dec 2006), it does recommend price regulation of almost all the 354 drugs in the National List of Essential Medicines (NLEM 2003). However as its own annexures reveal, almost all concerned ministries including the health ministry oppose the move.
[15] Akerlof, George A., "The Market for 'Lemons': Quality Uncertainty and the Market Mechanism." *Quarterly Journal of Economics,* 84(3), pp. 488-500, 1970
[16] Edward Glaeser in "The Marketplace of Perceptions", *Harvard Magazine,* March-April 2006. Also at www.harvardmagazine.com/on-line/030640.html.

[17]Figures quoted from *Pharmabiz* editorial. P A Francis "OPPI's Marketing Code", January 31, 2007.

[18] "Cough medicine brands are biggest sellers" by Rupali Mukherjee at http://timesofindia.indiatimes.com/articleshow/1411283.cms
[19] Another reason irrational and often expensive treatment occurs is due to the presence of cut practice, that is, kickbacks offered by specialists, pathologists, X-ray clinics, CAT scan centers, etc., to prescribers who refer patients to them.
[20] C M Gulhati. " Irrational fixed-dose drug combinations: a sordid story of profits before patients".*Indian J of Medical Ethics* at <http://www.issuesinmedicalethics.org/111ed005.html>.

[21] Worldwide sales of VIOXX in 2003 were $2.5 billion, making it a blockbuster for Merck.
[22] Rofecoxib belongs to the group of NSAIDs (nonsteroidal anti-inflammatory drugs) known as COX-2 selective inhibitors or coxibs (CycloOXygenase-2 InhiBitors). Being COX-2 selective means that these drugs act specifically on one form of the cyclooxygenase (COX) enzyme, namely the COX-2, whereas previous NSAIDs inhibited both COX-1 and COX-2. This specificity allows rofecoxib and other COX-2 inhibitors to reduce inflammation and pain while minimizing undesired gastrointestinal adverse effects - peptic ulcers - that are common with non-selective NSAIDs such as aspirin, naproxen, and ibuprofen. It is currently unknown whether the increased risk of adverse cardiovascular events is common to all COX-2 inhibitors.
[23] See Chapter 5 for a brief discussion on clinical trials, randomization, etc.
[24] *Adenoma* refers to a collection of growths (-oma) of glandular origin. Adenomas can grow from many organs including the colon, adrenal, pituitary, thyroid, etc. These growths are benign, but some are known to have the potential, over time, to transform to malignancy (at which point they become known as adenocarcinoma.) A *polyp* is a smooth-coated abnormal growth (tumor) projecting from a mucous membrane. It is attached to the surface by a narrow elongated pedicle. Polyps are commonly found in the nose, urinary bladder, uterus, rectum, and large intestine. They may also occur elsewhere in the body where mucous membrane exists. In 2001, Merck commenced the APPROVe (Adenomatous Polyp PRevention On Vioxx) study, a three-year trial with the primary aim of evaluating the efficacy of rofecoxib for the prophylaxis of colorectal polyps. Celecoxib had already been approved for this indication, and it was hoped to add this to the indications for rofecoxib as well. An additional aim of the study was to further evaluate the cardiovascular safety of rofecoxib.

The APPROVe study was terminated early when the preliminary data from the study showed an increased relative risk of adverse thrombotic cardiovascular events (including heart attack and stroke), beginning after 18 months of rofecoxib therapy. In patients taking rofecoxib, versus placebo, the relative risk of these events was 1.92 (rofecoxib 1.50 events vs placebo 0.78 events per 100 patient years). The results from the first 18 months of the APPROVe study did not show an increased relative risk of adverse cardiovascular events. (Bresalier *et al*., 2005). Previous Phase III clinical trials had also not shown this trend. (Swan, 2004) In sum, the APPROVe study suggested that long-term use of rofecoxib resulted in nearly twice the risk of suffering a heart attack or stroke compared to patients receiving a placebo.

[25] "Conflicts of Interest on COX-2 Panel" at <http://www.cspinet.org/integrity/press/200502251.html>:

"The Food and Drug Administration on February 16-18, 2005 held an advisory committee meeting to discuss the cardiovascular risk posed by painkillers known as Cox-2 inhibitors, which include Celebrex, Bextra and Vioxx. The former two drugs are manufactured by Pfizer. The latter is manufactured by Merck. Novartis also has a Cox-2 inhibitor in its pipeline. At the end of the hearing, the FDA advisory panel voted to keep all three on the market, though with heightened warnings about the dangers posed by this class of drugs. At the request of the New York Times, the Center for Science in the Public Interest evaluated the 32 scientific experts chosen by the FDA to evaluate these drugs. The CSPI research uncovered affiliations between 10 of the scientists that served on the committee and the three manufacturers of Cox-2 inhibitors. This would appear to be a direct violation of the Federal Advisory Committee Act, which prohibits scientists with direct conflicts of interest from serving on panels offering advise to federal regulatory agencies. Another 17 scientists had other ties to drug manufacturers, though not the three with products under consideration at the meeting. According to a *New York Times* analysis of the votes, the advisory committee would have voted against Bextra and Vioxx staying on the market had scientists with conflicts of interest been excluded from the vote."

[26] Source: < http://gastroenterology.jwatch.org/cgi/content/full/2005/1230/11>
[27] For the testimony of Dr Graham before the Senate Finance Committee, see Annexure 6: "Rofecoxib, Heart Attacks and the FDA: Testimony of David J. Graham, MD, MPH, November 18, 2004". See also at the FDA website, <www.fda.gov/cder/drug/infopage/vioxx/vioxxgraham.pdf >, "Memorandum from David J. Graham, MD, MPH, Associate Director for Science, Office of Drug Safety to Paul Seligman, MD, MPH, Acting Director, Office of Drug Safety entitled, 'Risk of Acute Myocardial Infarction and Sudden Cardiac Death in Patients Treated with COX-2 Selective and Non-Selective NSAIDs', September 30, 2004."

[28] See "Conflicts of Interest on COX-2 Panel" at <http://www.cspinet.org/integrity/press/200502251.html>

[29] As of Nov. 30, 2005, Merck reported that it has been served or is aware that it has been named as a defendant in approximately 9,200 lawsuits, which include approximately 18,250 plaintiff groups alleging personal injuries resulting from the use of the drug. In addition, as of Nov. 30, 2005, approximately 3,700 claimants had entered into Tolling Agreements with the Company, which halt the running of applicable statutes of limitations. And it is not just the United States victims that are suing the company. The Australian law firm, Slater and Gordon, has sued Merck in the Supreme Court of Victoria seeking damages for at least 400 victims, including family members of approximately 50 who died while taking the drug. Australian lawyers say that the number in Australia could reach into thousands.

[30] Source: *Journal Watch Gastroenterology*, December 30, 2005.
[31] This part is from previously published by Anurag Bhargava in *Impoverishng the Poor*, op.cit.
[32] "Belittling of a High Office" June 27, 2000, Editorial, <www.pharmabiz.com>
[33] See "Study on Haematinic Formulations Marketed in India", *BODHI*, Vol 10, No 2, May-June 2002
[34] Some useful references for the details of the debate are:

- Jacob John T. "End-Stage Challenges Vaccine-associated paralytic poliomyelitis."
- *Bulletin of the World Health Organization.* January 2004, 82 (1).

- Jacob John. T. "Polio Eradication: A National Commission Required." *Economic and Political Weekly*, December 23, 2006

- C.Sathyamala, Onkar Mittal, Rajib Dasgupta, Ritu Priya, "Polio Eradication
- Initiative in India – Deconstructing the GPIE." *International Journal of Health Services,*
- Vol. 36, Number 2, 2005, P.363

- Sathyamala et al in "Polio Eradication Initiative at what cost", in Sujata Prasad and C.Sathyamala (ed.) *Securing Health for Al: Dimensions and Challenges*. Institute for Human Development, New Delhi, pp. 269-286

- Yash Paul. "Polio Eradication Programme: A Failure." *Economic and Political Weekly.* November 4, 2006

- Yash Paul and Angus Dawson. "Some Ethical Issues Arising from Polio Eradication Programmes in India." *Bioethics,* Volume 19 Number 4 2005

- Anant Phadke et al in: Jan Swasthya Abhiyan *New Technologies in Public Health – Who pays and who benefits?* January 2007.

[35] All these quotes are from: Y. Paul. "Polio eradication: experts have misled us." *Medical Veritas* 3 (2006) 781–785. Also in: Yash Paul. "Polio Eradication Programme: A Failure." *Economic and Political Weekly*, November 4, 2006.

[36] *New Technologies in Public Health,* op.cit., pp. 37 ff.

[37] This section has been paraphrased from Phadke et al in *New Technologies in Public Health – Who pays and who benefits*, op.cit. pp.41 ff. And almost verbatim from "Letter to Health Minister on Hepatitis B Vaccine: Why we don't need to give it for all newborns", *mfc bulletin,* Oct 2005-Jan 2006. References given these are not cited in the current chapter.

[38]Phadke Anant, Kale Ashok. HBV Carrier Rate in India. *Indian Pediatr* 2002; 39: 787.

[39]The figure of 4.7 % is from: S.P.Thyagarajan, S.Jayaram, B. Mohanvalli. Prevalence of HBV in the General Population of India, in *Hepatitis B in India*, (Ed.) S.K.Sarin, A.K.Singhal, CBS Publishers & distributors, 1996, page 9. Phadke and Kale, op.cit., show that this figure is an over estimate as the authors have made the elementary mistake of averaging the averages of different studies. The correct average turns out to be 2.7 % which has to be multiplied by the positivity factor of 67 % (all those found positive in blood tests may not have the infection. In fact only 67 % normally do so. That is the positivity rate is 67 %.) to arrive at the correct estimate of the prevalence rate of 1.77 %. The authors Thyagarajan et al have glossed over this fact as also the fact that all of the 1.77 % would not have chronic Hep B infection and assumed that everybody who is found positive in blood test may not necessarily have not necessarily have the infection. Chronic Hepetitis B infection means persistence of Hep-B infection after 6 months or more. Normally only 80 % of those identified as carriers continue to test positive. So the prevalence rate turns out to be even less: 1.77 % x 0.80 = 1.42 %.

[40] "If this vaccine is given intra-dermally - i.e., within the two layers of the skin, only one-fifth the dose is sufficient and yet the resistance acquired to Hepatitis-B infection is equally good. Studies in India have also proved this (A study in infants has also shown this). But the concerned companies are silent about this Intra Dermal route for hepatitis-B vaccine - because this will reduce their sale by 80% ! Even amongst all the doctors who are for Hepatitis-B for every infant do not talk about this I.D. route, because most of them rely on the drug companies for updating their knowledge. Our paramedics have been giving intra dermal BCG vaccine for millions of infants every year. Hence giving Hepatitis-B vaccine intra-dermally to infants would not be problem. It should be noted that even if we reduce the expense of the vaccine by 80% the cost-efficacy of Hepatitis-B vaccine may not match with that of the existing vaccines in the National Immunization Programme." Phadke et al, op.cit., p. 54.

[41] Hernan M A, Jick SS, Olek MJ, Jick H. "Recombinant Hepatitis B vaccine and risk of multiple sclerosis." *Neurology* 2004; 63:838:42. Quoted in Phadke et al, op.cit., p. 53.

[42] Phadke, et al. page 41.

[43]Source: "Unending Q of Unethical Drug Trials," Editorial in *MIMS Inida*, Feb 2004. See also: Nundy, Samiran and Gulhati, Chandra M. "A New Colonalism? –Conducting Trials in India". *N Engl.J Med* 352; 16, April 21, 2005. See also Gulhati's article in the *Indian Journal of Medical Ethics,* Jan-Feb 2004.

[44] "Johns Hopkins admits scientist used Indian patients as guinea pigs". *BMJ* 2001; 323:1204 (24 November). Also see: "The truth of the 'drug' trials". *Frontline,* Volume 18, Issue 24, Nov. 24 - Dec. 07, 2001.

[45] "A Case of Betrayal", *Frontline,* Volume 22 - Issue 25, Nov. 05 - 18, 2005. In the same issue a related report, "A award and some claims" reported:

An innocuous statement published in a few newspapers in July should have caused a sensation in India and abroad. But it did not.

It was issued by Dr. M. Krishnan Nair, the former Director of the Regional Cancer Centre, Thiruvananthapuram, to announce that a scientific paper titled `Five year survival results of a single group study of intralesional tetra-O-methyl nordihydroguiaretic acid in oral squamous cell carcinoma (M4N study)" has been awarded the `Best Clinical Award' in the 10th International Congress on Oral Cancer held in the Island of Crete in Greece and the authors have been awarded a cash prize of 1000 euros.

"In this particular study the authors were able to obtain the best relapse-free survival at five years compared to all historic data on this cancer that too with a short exposure to M4N. The Food and Drug Administration of USA has approved this drug for clinical use," the note sent to newsrooms on July 7 said.

It ended cryptically, explaining the significance of the award: "It may be noted that a great hue and cry was raised by two doctors in Regional Cancer Centre along with a few members of the lay public in the media in Kerala about the use of this drug."

[46] *MIMS India*, op.cit.

[47] Full text available at <http://finance.senate.gov/hearings/testimony/2004test/111804dgtest.pdf>. Reproduced in full as Annexure 6, Chapter 3 of this book.

[48] Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. "Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events?" *JAMA.* 2003 Aug 20;290(7):921-8

[49] Bhandari M. etal. "Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials." *CMAJ.* 2004 Feb 17;170(4):477-80

[50] Ridker PM and Torres J. "Reported outcomes in major cardiovascular clinical trials funded by for-profit and not-for-profit organizations: 2000-2005." *JAMA* 2006 May 17; 295(19):2270-4. "Of the 324 superiority trials, 21 cited no funding source. Of the 104 trials funded solely by not-for-profit organizations, 51 (49%) reported evidence significantly favoring newer treatments over the standard of care, whereas 53 (51%) did not (P = .80). By contrast, 92 (67.2%) of 137 trials funded solely by for-profit organizations favored newer treatments over standard of care (P<.001). Among 62 jointly funded trials, 35 (56.5%), an intermediate proportion, favored newer treatments. For 205 randomized trials evaluating drugs, the proportions favoring newer treatments were 39.5%, not-for-profit; 54.4%, jointly funded; and 65.5%, for-profit trials (P for trend across groups = .002). For the 39 randomized trials evaluating cardiovascular devices, the proportions favoring newer treatments were 50.0%, not-for-profit; 69.2%, jointly funded; and 82.4%, for-profit trials (P for trend across groups = .07). Regardless of funding source, trials using surrogate end points, such as quantitative angiography, intravascular ultrasound, plasma biomarkers, and functional measures were more likely to report positive findings (67%) than trials using clinical end points (54.1%; P = .02). CONCLUSIONS: Recent cardiovascular trials funded by for-profit organizations are more likely to report positive findings than trials funded by not-for-profit organizations, as are trials using surrogate rather than clinical end points. Trials jointly funded by not-for-profit and for-profit organizations appear to report positive findings at a rate approximately midway between rates observed in trials supported solely by one or the other of these entities."

[51] Jorgensen AW, Hilden J, Gotzsche PC. "Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review." *BMJ.* 2006 Oct 14; 333 (7572):782.

[52] "Drug firms accused of distorting research", September 10, 2001, *The Guardian*. For the complete statement see, "Sponsorship, Authorship, and Accountability", *JAMA*, Vol. 286, No. 10, September 12, 2001 and at <http://jama.ama-assn.org/issues/v286n10/ffull/jed10056.html>. The signatories were: Frank Davidoff, MD editor emeritus, *Annals of Internal Medicine*; Catherine D. DeAngelis, editor, *JAMA*, MD, MPH; Jeffrey M. Drazen, MD, editor-in-chief, *New England Journal of Medicine*; John Hoey, MD, editor, *Canadian Medical Association Journal*; Liselotte Højgaard, MD, DMSc, editor-in-chief, *Tidsskrift for Den*

norske laegeforening (*Journal of the Norwegian Medical Association*); Richard Horton, FRCP, editor, *The Lancet*; Sheldon Kotzin, MLS, executive editor, MEDLINE/Index Medicus; M. Gary Nicholls, MD, editor, *New Zealand Medical Journal*; Magne Nylenna, MD, editor-in-chief, Norwegian Medical Association; A. John P. M. Overbeke, MD, PhD, executive editor, *Nederlands Tijdschrift voor Geneeskunde* (*Dutch Journal of Medicine*); Harold C. Sox, MD, editor, *Annals of Internal Medicine*; Martin B. Van Der Weyden, MD, FRACP, FRCPA, editor, *The Medical Journal of Australia*; Michael S. Wilkes, MD, PhD, editor, *WJM Western Journal of Medicine.* The authors were members of the International Committee of Medical Journal Editors.

[53] Statement by 13 editors, op.cit.

[54] Reported in *The Guardian*, as cited before.

[55] Statement by 13 editors, op.cit.

[56] Horton R. "The Dawn of McScience". *New York Rev Books*. 2004; 51(4):7-9. Quoted in Smith, op.cit.

[57] Richard Smith. "Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies." *PLOS*, Vol 2, Issue, May 2005. And at <http://medicine.plosjournals.org>

[58] a) Rochon PA, Gurwitz JH, Simms RW, Fortin PR, Felson DT, et al. (1994). "A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis." *Arch Intern Med* 154: 157–163.

b) Lexchin J, Bero LA, Djulbegovic B, Clark O (2003). " Pharmaceutical industry sponsorship and research outcome and quality." *BMJ* 326: 1167–1170.

[59] Quoted in: Ida Sim and Don E. Detmer. "Beyond Trial Registration: A Global Trial Bank for Clinical Trial Reporting". *PLOS,* Volume 2, Issue 11, Nov 2005.

[60] New York Supreme Court (2004). People of the State of New York v. GlaxoSmithKline. New York: New York Supreme Court. Available online.

[61] 1) Topol EJ (2004). "Failing the public health—Rofecoxib, Merck, and the FDA." *N Engl J Med*, 351: 1707–1709.

2) Mathews A, Martinez B (November 1, 2004). "E-mails suggest Merck knew Vioxx's dangers at early stage." *Wall Street Journal* Sect A 1.

3) Psaty BM, Furberg CD (2005). "COX-2 inhibitors - Lessons in drug safety". *N Engl J Med*, 352: 1135–1135. All above references quoted in Sim and Detmer op.cit.

4) "Documents Suggest Merck Tried to Censor Vioxx Critics" at <http://www.npr.org>

[62] <http://www.vaccinationnews.com/DailyNews/June2002/CriticsSay26.htm>. See also "Phase IV Trials – Real and Bogus" in *The Truth about the Drug Companies*, Chapter 9, pp.161 ff.

[63]Affidavit of Gurkirpal Singh, MD (Adjunct Clinical Professor of Medicine
Department of Medicine, Division of Gastroenterology, Stanford University School of Medicine and Chief Science Officer, Institute of Clinical Outcomes Research and Education), Senate hearing on Vioxx. Online at <http://finance.senate.gov/hearings/testimony/2004test/111804GStest.pdf>.

[64] Joel R Lexchin. "Implications of Pharmaceutical Industry Funding on Clinical Research." *Ann. Pharmacother.*, Jan 2005; 39: 194-197.

[65] op.cit., pp.50-51

[66]"Illegal, Unethical Promotion Hits New Highs: Indications Increased, Side Effects Suppressed", *MIMS India*, July 2005, Editorial. See also "Piracetam and Down Syndrome" at <http://www.ds-health.com/piracet.htm>.

[67] Source: *MIMS India*, July 2005, Editorial, op.cit.

[68] "Heptatitis-B firms get a shot in the arm: Centre's move to include vaccine in national immunisation plan to boost demand 300%." *Business Standard, Sep 15, 2005*. See also "Letter to Health Minister on Hepatitis B Vaccine: Why we don't need to give it for all newborns". *mfc bulletin,* Oct 2005-Jan 2006.

[69] This and the next four instances are from: Parry, Vince. "The Art of Branding a Condition." *Medical Marketing & Media*, May 1, 2003. Quoted also in *BODHI,* 57, Mar-Apr 2004, Editorial, "Branding Human Miseries". Also available at <http://offlinehbpl.hbpl.co.uk/Misc/MMM/Features/CONDITION.pdf>.

[70] "Serotonin and Depression: A Disconnect between the Advertisements and the Scientific Literature", *PLOS Medicine,* Volume 2, Issue 12, December 2005.

[71] In 1965, Joseph Schildkraut put forth the hypothesis that depression was associated with low levels of norepinephrine and later researchers theorized that serotonin was the neurotransmitter of interest.

[72] Kravitz RL, Epstein RM, Feldman MD, Franz CE, Azari R, et al. (2005) "Influence of patients' requests for direct-to-consumer advertised antidepressants: A randomized controlled trial". *JAMA* 293: 1995–2002. Quoted in Lacasse and Leo, op.cit.

[73] Valenstein ES (1998). *Blaming the brain: The truth about drugs and mental health.* New York: Free Press. 292 p. Quoted in Lacasse and Leo, op.cit.

[74] Lacasse and Leo, op.cit.
[75] Parry. op.cit.
[76] This and the following two examples are from: Ray Moynihan, Iona Heath, David Henry, and Peter C Gøtzsche. "Selling sickness: the pharmaceutical industry and disease mongering". *BMJ* 2002; 324:886-891 (13 April). See also: Ray Moynihan and Alan Cassels, *Selling Sickness: How the World's Pharmaceutical Companies are Turning us into Patients*. New York: Nation Books, 2005.
[77] See<http://www.fda.gov/cder/drug/infopage/lotronex/lotronex.htm> as also <http://www.injuryboard.com/view.cfm/Topic=640>
[78] "Pharmaceutical giants hire ghostwriters to produce articles - then put doctors' names on them ", Antony Barnett, public affairs editor, December 7, 2003, *The Observer*, and at <http://observer.guardian.co.uk/uk_news/story/0,6903,1101680,00.html>
[79] "Medical journals and pharmaceutical companies: uneasy bedfellows" in *BMJ*, 31st May 2003 (Vol 326, issue 7400), Richard Smith, *editor,* <http://bmj.bmjjournals.com/cgi/content/full/326/7400/1202>.
[80] Richard Smith, op.cit.
[81] 1. Hock C, *et al.* Report: "Antibodies against □-Amyloid Slow Cognitive Decline in Alzheimer's Disease". *Neuron.* 38, 547-554 (22 May 2003).
2. Winblad B, Blum KI. Preview: "Hints of a Therapeutic Vaccine for Alzheimer's?" *Neuron.* 38, 517-8 (22 May 2003)
[82] "Medical journals and pharmaceutical companies: uneasy bedfellows" in *BMJ*, op.cit.
[83]A more complete quote of Vinay Lal. ["Home Truths and McData". *The Little Magazine.* Vol V: Issue 4 & 5, 2004] would be: "…from under conditions of globalization Western knowledge systems have sought, largely with success, to gain complete dominance across the globe in nearly all spheres of life. The economists' conceptions of growth, poverty, scarcity, and development, marketed by all the social sciences, have come to predominate everywhere, and the sum total of Western social science has not only been to mire the so-called developing world in ever more acute levels of poverty, but to forestall the possibility of worldviews and lifestyles that do not synchronize with the conception of the "good life" that prevails in the "developed" West. The entire theory of development…is predicated on a time-lag: countries that are under-developed or part of the developing world seek to emulate the developed countries, but by the time they have seemingly caught up, the developed countries have gone well beyond to another plane of development. The natives, to speak in a different tongue, always arrive late at the destination; indeed, the theory of development condemns the underdeveloped to live not their own lives, but rather to fulfill someone else's conception of life. Development doesn't merely demand that the past of the native be entirely jettisoned, it also hijacks the native's future."
[84]Quoted in *Against Intellectual Monopoly*, Michele Boldrin, and David K. Levine, online at <www.dklevine.com/general/intellectual/against.htm>, Nov 2005).
[85] The reference is to the Novartis battle in the courts for monopoly status over the blood cancer drug Gleevec (imatinib mesylate). Novartis has challenged India's patent law in the Chennai High Court, arguing that it is unconstitutional as well as in breach of international trade law. This action of Novartis follows rejection of its patent application for the cancer drug Gleevec (Imatinib mesylate) by the Controller General of Patents and Designs, Chennai, in January 2006, on grounds that the product was not innovative enough. For details see, http://www.centad.org/.

[86] Report of the Technical Expert Group on Patent Law Issues, December 2006. The Terms of Reference of this committee headed by Mashelkar were : a) whether it would be TRIPS compatible to limit the grant of patent for pharmaceutical substance to new chemical entity or to new medical entity involving one or more inventive steps; and b) whether it would be TRIPS compatible to exclude micro-organisms from patenting.

[87] See Chan Park and Achal Prabhala."First attempt to dent a compromised patent system." At http://www.hindu.com/2007/02/12/stories/
[88] For WHO perspective on counterfeit medicines, see <http://www.who.int/medicines/services/counterfeit/overview/en/>. The website says: "The United States Food and Drug Administration estimates that counterfeits make up more than 10% of the global medicines market and are present in both industrialized and developing countries. It is estimated that up to 25% of the medicines consumed in poor countries are counterfeit or substandard. These figures place the annual earnings from the sales of counterfeit and substandard medicines at over US$ 32 billion globally. Trade in these medicines is more prevalent in countries with weak drug regulation control and enforcement, scarcity and/or erratic supply of basic medicines, unregulated markets and unaffordable prices. However, one of the most counterfeited drugs today is Viagra, which is sold extensively via the Internet in industrialized countries. A World Health Organization (WHO) survey of counterfeit medicine reports from 20 countries

between January 1999 to October 2000 found that 60% of counterfeit medicine cases occurred in poor countries and 40% in industralized countries."

[89] See also "Guidelines for the development of measures to combat counterfeit medicines" at <http://www.who.int/entity/medicines/publications/counterfeitguidelines/en/index.html>
[90] Source: <http://www.financialexpress.com/columnists/full_column.php?content_id=27319>
[91] House of Commons Health Committee. *The Influence of the Pharmaceutical Industry, Volume* I, Report, together with formal minutes. Fourth Report of Session 2004–05. Available at <www.parliament.uk/parliamentary_committees/health_committee.cfm>. Hereafter, House of Commons Report on *The Influence of the Pharmaceutical Industry*, 2004-05.

[92] See also for instance Chapter 6, "How Good Are New Drugs?" in Angell, Marcia. *The Truth About the Drug Companies: How they deceive us and what they do about it.* Random House, New York, 2004.
[93] One should add here we are talking of scientific rationality as understood in modern medicine. While there are problems in the construction of this rationality, specifically in the interpretation of evidence and in the conduct of clinical trials, there is no dispute among its adherents that it is a desirable thing. The economist's idea of rationality means consistent behaviour in pursuit of a goal and this goal usually for corporates is maximization of wealth. Pharma companies in this world of the rationality of the bottom-line, somewhat decidedly irrational for many of us pursuing other goals like minimizing illness and suffering, are definitely rational in the economist's sense of the term. Herbert Simon, Amartya Sen and now behavioral economists, among others, have provided critiques of the economist's idea of rationality.
[94] But actually it is barrier building by free traders of the Empire so that the poorer countries do not trade with comfort. Also the fear of "what if these poor quality drugs slide into our advanced countries." Both these barriers have been demolished by eager third world homo economicus types although the fears of the first world remain of being overtaken. Inscrutable are the ways of globalization and its worshippers.
[95] See quote of Hayek further below.
[96] After Wittgenstein
[97] That is theory, and our language, determine our hypotheses and what we are looking for in trying to make sense of "our" experiences and the "data" we collect. In blissful ignorance of Haldane's observation that the universe is not only stranger than we imagine but stranger than what we can imagine.
[98]At the risk of appearing whimsical, why is unaffordability not a side-effect or denial of access not an adverse drug reaction?

[99] Of course Hayek's defence of free market and what he called decentralized market socialism was far more nuanced than the above quote suggests.