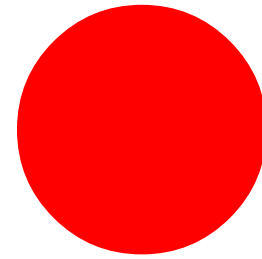


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June-July 2008

Vaccine PSUs: Chronicle of an Attenuation Willfully Caused

*-Y.Madhavi**

The recent suspension of production in three vaccine Public sector Units (PSUs)¹ in favour of setting up of a new vaccine park in Chingelput^{2,3} by the Ministry of Health and Family Welfare of the Government of India reveals how indigenous efforts to achieve self-sufficiency (one of the stated policy objectives) in vaccine production has been jeopardized, especially at a time when there is a short supply of primary vaccines globally. Vaccine production has been stopped abruptly in three existing public sector vaccine units (PSUs), due to WHO-inspired objections by the National Regulatory Authority (NRA) [for India the NRA is the Drug Controller General of India, DCGI], regarding the alleged failure of the PSUs to comply with the norms of “Good Manufacturing Practices” (GMP). These are: the Central Research Institute (CRI, Kasauli, HP), Pasteur Institute of India (PII, Coonoor, TN) and the BCG Vaccine Lab, (BCGVL, Guindy, TN). These units produced all the primary vaccines (except for measles) that are needed for the Indian Government’s universal immunization programme (UIP), also known as Expanded Programme of Immunization of (EPI) meant to protect the 26 million Indian newborns every year. It is quite surprising that these PSUs have been asked to stop production even before the proposed centralized GMP-compliant vaccine park becomes operational at Chingelput (Chengalpattu), Tamilnadu. It is even more interesting to note that the very same Government that has failed to respond to the PSUs’ modernization needs and GMP compliance etc. now accepts the WHO blame that they are non-compliant and halts production. Ironically, this is happening at a time when their productions have peaked and the vaccine demand-supply gaps are narrowing down, and there has been no complaint at all on the quality of the vaccines

produced. It is not much of a consolation that the Government does not intend to close these units and use them as testing labs or protect the jobs of the employees. The wisdom of creating a whole new centralized Vaccine Park at Chennai, while allowing the existing assets to languish is questionable on grounds of good governance and economic prudence. How the Government plans to handle the huge shortfall for vaccines till new production facilities come up at the vaccine park (estimated by 2011) is anybody’s guess.

Lingering Questions

These fast developments have put India’s universal immunization programme under crisis. It is reported that many states have run out of their supplies and the Government has not allowed them to pick up even the existing stocks from the PSUs. The first question that would arise is how does the Government meet the demand-supply gap of EPI vaccines till the new vaccine park starts production by 2011, especially at times when there is a short supply of primary vaccines world over <http://www.unicef.org/supply/index_vaccine_security.html> with very few EPI vaccine manufacturers. Secondly, what is the guarantee that another public sector unit, Hindustan Latex Limited (HLL) that does not have any expertise in vaccines whatsoever (except that it mediated occasional import of some vaccines to the Government), would be able to manufacture quality vaccines and remain WHO GMP compliant for ever? Thirdly, what is the guarantee that HLL would not meet the same fate as these 3 public sector units in near future? Fourthly, if such a situation arises in future, how is the Government going to tackle similar crisis once again? Is it through imports or is it through private sector, and if so, from whom and at what price and how much would it cost the Government to immunize 26 million children born annually? Has there been any economic evaluation of such issues? What is the

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economic logic of spending over Rs 150 crores on building a new vaccine park when modernizing existing PSUs would have cost less than Rs 50 crores? Will the new companies that will come up in the vaccine park really manufacture the vaccines indigenously or repackage them from imported bulk? If they import, what is the point in achieving GMP compliance at the cost of indigenous manufacturing ability? If dependence on private sector supply or import is inevitable, how will the Government tackle concerns of biosecurity and strategic national health security? The answers to many of these questions are implicit in the trajectory of developments that led to the current crisis of vaccine PSUs. The basic theme may be familiar for most PSUs in India, yet each case is unique.

Committed and Dependable Service

CRI Kasauli (1905) and PII Coonoor (1907) are more than 100-year old and the BCG Vaccine Laboratory (BCGVL) Chennai (1948) is 60-year old. They formed the very foundation of modern medical research in India and did committed and dependable service to the nation for all these decades, despite the failure of successive Governments to nurture R&D capabilities and technological growth in favour of shortsighted production targets. These institutions did some research to develop technologies, process innovations, methods etc., to improve the yields and potency of vaccines and sera with whatever minimum resources were available to them. CRI Kasauli prides itself of being the first laboratory in the world to produce Anti-Rabies vaccine under the guidance of its first Director, David Semple.³ The Institute produces vaccines against Diphtheria, Tetanus, Pertussis, Yellow Fever, Typhoid, Japanese Encephalitis and Anti-Sera against Diphtheria, Tetanus, Rabies and Snake venoms, besides producing various diagnostic reagents <<http://mohfw.nic.in/kk/95/ib/95ib0q01.htm>>. CRI also has the additional function of quality control of vaccines and sera that are produced in the country before they are supplied to EPI and released into the market.

PII was the first institute in India to try out the value of antirabies serum-vaccine therapy in the treatment of human beings introduced in 1917 by its first director Cornwall. It also produced OPV vaccine indigenously with the seed virus obtained from Sabin during 1967-76. The institute developed tissue culture based anti-rabies vaccine in 1990s from sheep brain tissue rather than from mouse brain tissue as this was more economical as raw material. It also developed a cost-effective tissue culture-based Japanese encephalitis vaccine. PII did many innovations to reduce costs and increase the yield of DPT (Diphtheria, Pertussis, and

Tetanus) group of vaccines.⁴ PII introduced betapropiolactone-inactivated brain tissue rabies vaccine for the first time in the country in 1970s. It also manufactured DTP-Hepatitis B (DTP-HB), which was launched by the Health Minister in June 2007, along with modern quality control machinery and separate divisions for biotechnology and microbiology on its centenary day celebrations.³

BCGVL manufactured BCG vaccine from the seed virus obtained from the State Serum Institute, Copenhagen until 1993 and later it developed its own seed virus called Madras Working Seed Lot (MWSL). Since 2001, BCGVL became self-sufficient in its production as it increased its production capacity and in fact it earned revenue of Rs. 6.12 crores by selling it to private suppliers during the year 2001-02. BCGVL is the only institute that catered to the entire BCG vaccine requirement of the country and was the only institute under the Ministry of Health & Family Welfare, which obtained ISO 9002 Certification. BCGVL, did process innovations to improve sterility and yield at low cost. It also produces freeze dried therapeutic vaccine (40 mg) for cancer chemotherapy. It also serves as national quality control lab for BCG vaccine <<http://mohfw.nic.in/dghs1.html>>.

These instances prove that these PSUs had the inherent interest, will, ability and enthusiasm to remain productive, innovative and competitive. However, most of the Government support received by these units was for enhancing production capacities, rather than for upgrading infrastructure, R&D, technological growth and compliance to good manufacturing practices (GMP). To add to such lack of vision and neglect, there has been a systematic decline of the state patronage of PSUs, while bureaucratic controls and ministerial whims continued, if not worsened. Even the policies of economic liberalization in 1990s did not enhance the functional autonomy of the vaccine PSUs. On the contrary, supporting and reviving PSUs became politically unfashionable and blaming the PSUs and manufacturing political consent for their closure became the favourite pass time of the powers that be. Even many scholars who worked on the impact of liberalization, globalization, TRIPS and WTO on the pharmaceutical industry in India (which had already become almost entirely private by the 1990s), did not pay any attention to the vaccine sector, which was the last bastion of the public sector in the Indian Pharma industry. With such orphanisation, it was just a matter of time before some vested interest launched an opportune death blow. Operationally, starving and stifling PSUs till they failed to meet some regulatory requirements was a safe strategy, as the action taken

on the PSUs would seem like an act of good governance, rather than the lack of it.

GMP Comes Handy

The current crisis of suspending production in these 3 PSUs arose with the allegation that they are not WHO GMP compliant, though there were apparently no specific complaints on the quality of the vaccines produced. A GMP assessment committee under the WHO-NRA process constituted by the Health Ministry under the Drug Controller General of India (DCGI) inspected the facilities once in Aug 2007, Nov 2007 and in Jan 2008. The committee pointed out that the three units are non-compliant with the conditions, namely Rule 78, a (i), and Rule 78 p, of the Drugs & Cosmetics Act that has to do with maintaining adequate staff and adequate premises and plant, and the non-compliance of GMP as laid down under Schedule M of the same Rules. According to media reports, the institutes stated in their reply to DCGI that limited funds and lack of functional autonomy in recruitments, promotions, maintaining staff, finances, structure etc., and the lack of flexibility in running these biological industrial units due to bureaucratic limitations as the reasons for their inability to comply with the GMP norms. These PSUs could meet GMP standards earlier in 2001 and 2004. However, they could not meet them in 2007 as they were made more stringent. The stringent rules in the current GMP standards with which these institutions could not comply are said to be related to structural, process and documentation deficiencies. The institutes are said to have reported that while process deficiencies have been by and large rectified, structural and documentation deficiencies remained. It is not clear what efforts were made by the Health Ministry, which owns and governs the vaccine PSUs, to make them comply with the increasingly stringent GMP norms, before taking such a drastic action on them. It is also not clear whether such frequent inspections and stringent application of GMP norms were applicable only to vaccine PSUs or to the Pharma industry as a whole, since there seem to be many private Pharma companies that operate without GMP certification. The strange logic repeatedly offered by the Ministry is that WHO threatened to derecognize the Indian NRA if it did not take stringent action against the noncompliant vaccine PSUs and that it would have hit Indian exports even from the compliant industries. Firstly, it implies that export earnings (especially of the burgeoning private vaccine units) are more important than meeting indigenous vaccine needs and protecting indigenous manufacturing in PSUs. Secondly, it sounds as if these vaccine PSUs had all the functional and financial

autonomy needed to comply with the GMP and yet they did not. The reality seems to be the opposite, as reportedly argued by the PSUs themselves. Since it is the Health Ministry that owns and governs these units, by the same regulatory logic applied in its proper context, someone may argue that it is not the PSUs but those responsible in the Ministry for their inability to ensure GMP compliance should be suspended. After all, the buck stops with the boss.

This is not the first time that regulatory issues came up against vaccine PSUs. There have been instances in the past in PII Coonoor when OPV production was stopped, for eg., in 1976 on the advise of WHO, as one of the batches found to be reactogenic, PII was asked to restructure itself for the production of DPT group of vaccines from the same year, and OPV became one of our major vaccine imports since then.⁵ However, media reports indicate that a later test by S. Archetti of WHO found that particular batch of Indian OPV to be of excellent quality and that the toxicology report of NICD was faulty.³ Yet, indigenous OPV production was never revived. Similarly, one of the institutes wanted to grow monkey kidney cell culture for the indigenous production of OPV, but they were discouraged on the advice of WHO and it was only in late 1990s that Haffkine Biopharmaceuticals Ltd (HBPCL) was allowed to obtain seed virus from abroad for its indigenous production. Once again in 2000, Maharashtra State Government refused to buy OPV from HBPCL alleging that their vaccine was not potent and procured OPV from Radicura Pharma, a private company. HBPCL had to file a PIL against Maharashtra Government that it was a false allegation designed to favour a private company.⁶ Even the more recent ultramodern GMP-compliant vaccine PSUs that emerged during post 1990s under DBT (Department of Biotechnology) also faced regulatory hurdles, when UNICEF refused to accept OPV supplies from BIBCOL (Bharat Immunologicals and Biologicals Ltd) made from bulk imported from a Russian PSU, alleging that the vaccine from Russia was not WHO GMP compliant. India had no option but to import OPV bulk from Smith Kline Beecham (SKB) on the advice of WHO and only then BIBCOL was allowed to export the repackaged OPV to UNICEF.⁵ Therefore, even a modern PSU like BIBCOL that was certified WHO GMP compliant for the indigenous production of OPV could never manufacture the vaccine for some extraneous reason or the other, and continues to function as a repackaging unit. Given this background, there is no guarantee that the emerging HLL-led vaccine park at Chingelput would not meet the same fate as the other vaccine PSUs.

Goofy Management Practices: a new GMP Standard

The detailed media reports in *Frontline* and *Pioneer* clearly bring out that the decision of the DCGI to suspend production in the three vaccine PSUs based on the report of the WHO-NRA team had the blessings of the Union Health Ministry. The media reports as well as representations made by the Save Pasteur Institute of India Coonoor Association (SPIA) also brought out that the PSUs were not given enough time and the capital to meet the objections raised by the WHO-NRA team, despite repeated requests by these PSUs. Interestingly, the present DCGI who suspended production in the vaccine PSUs was earlier the Additional Director of CRI Kasauli, a person who could not make it GMP-compliant during his own time. Similarly, the same Health Ministry, which failed to respond in time to the GMP compliance needs of its units in turn blames them of noncompliance and justifies their suspension. Moreover, the same union Health Ministry that dragged its feet for a few tens of crore rupees to upgrade the existing PSUs for GMP compliance very generously sanctioned hundreds of crore rupees to set up a vaccine park in Chingelput. Ironically, the Ministry did not hesitate to import Japanese Encephalitis vaccine in 2006 from GMP non-compliant Chinese manufacturers. The Ministry is also aware that Chinese exports were neither hit due to their non-compliance, nor was the Chinese NRA derecognized by the WHO.⁷ Clearly, the Chinese Government seem to handle the WHO and its NRA better than the Indian Government.³

It seems that the stoppage of production in vaccine PSUs has been brewing for quite some time and the private industry has been preparing to capture the UIP vaccine market. This is evident from the fact that their production capacities for UIP vaccines have been enhanced over the last 3-4 years, unlike in earlier times when they were interested only in new and combination vaccines.³ The union Health Minister has been quoted as saying "The private sector WHO-certified GMP companies have committed on paper that they will meet the demand with better quality vaccines at the same price."³ Earlier, private sector companies like Shanta Biotech, Hyderabad, received huge soft-loans from the Technology Development Board of the DST (Department of Science and Technology) and the EXIM Bank for development of non-UIP vaccines, combination vaccines (DTP-HB) and other biopharmaceuticals.⁸ Shanta Biotech is now owned by a French MNC, the majority shareholder. Similar patronage was never enjoyed by any vaccine PSU so far.

More recent media reports have alleged dubious

dealings between some private companies and former director of the PII Coonoor and BCGVL and his wife, with the alleged support of the Health Ministry. A series of news items that appeared in *The Pioneer* daily between 10th May 2008 to till date (summarized below) raise serious questions of alleged corruption, favoritism and mismanagement that need criminal investigation.

□ The ex-director of BCGVL and PII Coonoor, Dr. N. Elangeswaran, who was a contender for the post of DCGI and was also meant to hold a senior position in the Vaccine Park at Chingelput, is said to have facilitated the decline of PII and BCGVL and the emergence of dubious private firms allegedly under pressure from the Health Ministry. Currently fallen out of the Ministry's favour and posted at CGHS Chennai as a senior microbiology specialist, he was said to have facilitated the transfer of crucial resources such as seed virus, guinea pigs, well-trained human resource to new private companies, especially Green Signal Bio Pharma, which was registered in 2005. This company is owned by Mr. Sundarapariipooran, who apparently belongs to Ramadoss' party PMK and is a close associate of the Health Minister. (*The Pioneer*, 10th May 2008)

□ Another Chennai-based new vaccine company called Vatsan Bio Pharma that came up in 2006 is also apparently co-owned by Mr. Sundarapariipooran and his wife, with the wife of Dr. Elangeswaran as a major shareholder. (*The Pioneer*, 10th May 2008)

□ On July 21st 2007 Dr. Elangeswaran allegedly stopped guinea pig breeding in the institute, which led to disruptions and stoppage of vaccine production. (*The Pioneer*, 16th May 2008)

□ WHO-NRA team visited PSUs in Aug 2007.

□ On 21st Sept 2007, an entire batch of 15 scientific staff of PII, recruited and trained under the direct supervision of the then director Dr. Elangeswaran, allegedly went missing from PII and defected overnight to Green Signal Bio , a clear case of unauthorized absence and no action was apparently taken against them by PII. In effect, PII recruited and trained staff for the benefit of a private company! (*The Pioneer*, 19th May 2008)

□ In Oct 2007, 600 guinea pigs were apparently ordered to be transferred from PII to BCGVL by the then director, Dr. Elangeswaran. However the consignment never reached BCGVL and was instead routed to a private vaccine manufacturer's compound in Mettupalayam. (*The Pioneer*, 16th May 2008)

□ WHO-NRA team visited PSUs in Nov 2007.

□ On 27th Dec 2007, Green Signal Bio Pharma apparently received a loan of Rs. 14 crore from Union Bank of India, Chennai, for starting the production of vaccines. The MOU signed between Green Signal Bio Pharma and BCGVL (by Dr. Elangeswaran) was hypothecated to obtain this loan. In other words, the then BCGVL director facilitated the bank loan as well as seed virus for Green Signal Bio Pharma.

□ The then PII director, Dr. Elangeswaran apparently gave the seed virus for polio vaccine production and DPT production free of cost to private companies, Bharat Biotech, Hyderabad and Serum Institute of India, Pune, respectively. (*The Pioneer*, 11th May 2008)

□ Trade union leaders alleged that for the past 4 years, the Health Ministry neither allotted funds to upgrade the PSUs, nor accepted WHO's offer to upgrade the technology in vaccine production. SPIA (Save Pasteur Institute Association) predicted that the vaccine price would increase 8-fold because of closure of PSUs and the entry of private sector.

□ SPIA alleged that Government-appointed officials helped private vaccine manufacturers in a well planned manner by murdering prestigious PSUs.

□ May, 2008: Ex-director of BCGVL apparently confessed that senior bureaucrats in Health Ministry pressurized him to close down the PSUs and to facilitate private companies for vaccine production (11th May, *The Pioneer*). They were later named to be Dr. Venkateswarlu, former DCGI and Mr. BK Prasad, Jt. Secy., in the Health Ministry. *Pioneer* later reported that both of them denied the allegations.

□ On 13th May 2008 Health Secretary apparently declared in a press conference that the govt. would initiate action against Dr. Elangeswaran for his "malicious allegations" against the Ministry. (14th May, *The Pioneer*)

□ On 17th May, 2008, *Pioneer* reported that the Ministry has given up the idea of taking action against Dr. Elangeswaran as the move might end up implicating many top shots, including the former DCGI and a joint secretary in the health department. The report also indicated that Dr. Elangeswaran may have fallen out with the Health Ministry when he was denied posting of DCGI, soon after he obliged the closure of vaccine production in the 3 PSUs.

□ Health Minister denied the allegation that he deliberately closed down the PSUs. According to him, a committee under DCGI would survey these three PSUs and submit the report in three months. The Minister also denied that he favoured any private firm

and denied that there were any requests from PSUs for upgradation. (18th May, *The Pioneer*)

□ 21st May 2008: A *Pioneer* report alleged that in late 2006, the Ministry ordered PII to stop producing the rabies vaccine (which PII has been producing for 100 years) and start manufacturing measles vaccines. On November 27, 2006, the then PII director, Dr. Elangeswaran, purchased measles seed from Green Signal Bio Pharma for Rs. 3.25 crores, which was otherwise available virtually for free from another PSU, Indian Immunologicals Institute, Hyderabad. The Health Ministry sanctioned PII Rs 17.80 crores for branching out into measles vaccine production only after it entered into the deal with Green Signal Bio Pharma. The entire deal was allegedly executed to help the private company, as it stipulates that the PSU would produce measles vaccines from the seed and give away 70 per cent of the profit to Green Signal Bio Pharma. The agreement was signed on November 27, 2007, and soon thereafter, Sundaraparipooranan withdrew Rs 2.5 crores. All the objections raised by the lower staff of the Health Ministry regarding Dr. Elangeswaran overshooting his financial powers and bypassing procedures were overlooked by the top functionaries of the Ministry. Interestingly, Green Signal Bio Pharma could purchase BCG seed from the PSU BCGVL (also headed at that time by Dr. Elangeswaran), for a mere Rs. 1.05 lakhs. This indicates that private firms get PSU resources for a song, whereas PSUs buy even free resources from favourite private firms by paying them the moon!

Political Countercurrents

Opposition leaders alleged that Parliament was not consulted about the closure of 3 PSUs. CPI (M) sought the Central Government's intervention in the revival of the vaccine PSUs and demanded a white paper from the Government on vaccine scam. A CPI(M) MP alleged that a move was afoot to sell the land under the 3 PSUs to completely dismantle these units for generating capital for recycling and to help new private companies like Green Signal Bio Pharma and Vatsan Bio Pharma to grab entire vaccine market from PSUs (*The Pioneer*, 13th May 2008). CPI (M) politburo member Brinda Karat also wrote a letter to the Health Minister to reconsider the review of PSUs and she feared that this closure would leave the field open for corporate Pharma companies and MNCs for the supply of vaccines required for UIP, which is certainly not in the national interest. She pointed that PSUs should be the core of public health programme, since the financial implications to upgrade the PSUs are not very substantial and also they have land to permit expansion. She questioned the wisdom of Health Ministry to close

down vaccine PSUs that have necessary expertise to produce vaccine and at the same time giving the job to another PSU HLL (Hindustan Latex Ltd) that does not have expertise in vaccines. Ms. Brinda Karat said that there is no answer to her queries till today from the minister (*The Hindu*, 13th and 23rd April 2008, and *The Pioneer*, 15th May 2008). BJP sought clarification from Prime Minister that the health minister was misusing his position by closing PSUs and helping private vaccine manufacturers. BJP claim though they are not against private manufacturers, but closing down PSUs under pressure from Health Ministry is a serious issue (Outlookindia.com, 17th May 2008, http://www.outlookindia.com/pti_news.asp?id=572191).

Conclusions and Recommendations

If the above chronology of events that were reported in *The Pioneer* is true, **it indicates a conspiracy to attenuate the PSUs in the name of GMP and benefit private firms in the name of meeting the vaccine shortages and protecting children.** A few months before the PII Coonoor was asked to stop production, there were apparent efforts to divert its main focus from rabies and DPT vaccines (its main forte for many decades) to Hep B-DPT combinations, measles, etc., under dubious deals with private firms. Critical resources of PSUs such as vaccine seed, technology, manpower training, guinea pigs, even money (that is not easily available from the Ministry for PSUs' own needs) have been passed on to private firms with competing interests and the Ministry did not seem to have stopped this, even if it did not stimulate or facilitate it. The mysterious deaths of 4 children (apparently due to brain hemorrhage) in Tamil Nadu after vaccination with measles vaccine supplied by Human Biological Institute, a public sector company under the Indian Immunological Institute, Hyderabad, out of 20,000 children vaccinated with the same batch <<http://www.thehindu.com/2008/04/24/stories/2008042457410100.htm>>; and the immediate halting of measles vaccine supply to all the districts - sounds even more mysterious in the midst of all these happenings. Apparently the measles vaccine quality was fine and nothing went wrong with the cold storage, keeping the puzzle unsolved. (Data source: <<http://www.thehindu.com/2008/05/16/stories/2008051660031200.htm>>

According to SPIA (Save Pasteur Institute Association), India's vaccine PSUs produce 90 % of the national total vaccine output, 70% of DPT and 100% of BCG vaccine. India is one of the largest suppliers (40-60%) to the world. The attenuation of PSUs will severely affect the indigenous manufacturing capability. Some of the remaining vaccine PSUs have

already become importers and repackaging units over the years. Even if the new vaccine park is led by another PSU, Hindustan Latex simply does not have the technology, experience or credibility to manufacture world-class vaccines as compared to any of the Indian vaccine PSUs. According to the article of R. Ramachandran in *Frontline*, the Minister admitted that Hindustan Latex is likely to go down the same path of bottling and repackaging of imported stocks or enter into the public-private partnerships. If the above examples of PPP (public private partnership) with Green Bio Pharma and Vatsan Biopharma are anything to go by, the future of Indian vaccine industry, policy and practice is not difficult to imagine. It is an irony that India is killing its vaccine PSUs at a time when countries like US, UK, and other developed European countries that had allowed their vaccine production to drift into the hands of private sector earlier have now seriously started reviving the public sector. Private sector can be complementary to public sector with good governance in place, but it cannot be a replacement in view of national public health and bio security concerns.

In order to ensure a stable and affordable supply of vaccines to immunize over 25 million children born every year, we need the strong presence of the public sector to keep the prices low and to achieve effective public health. An ideal vaccine policy that aims to achieve the stated goals of self sufficiency and self reliance should have the following elements: 1) Indigenous manufacturing of all 6 universally administered (EPI) vaccines, ideally reserved exclusively for the public sector. Alternatively, the presence of at least two PSUs per vaccine (as a backup for each other) as a deterrent against market vagaries. 2) Investments for infrastructure modernisation, R&D etc in each of the vaccine PSUs and functional autonomy. 3) Advance market commitment by the Government to purchase vaccines made in PSUs is a must (purchase guarantees are commonly given to private and foreign firms in the name of boosting investments, but public sector never gets any guarantees or comparable prices from the Government). 4) Any private sector unit that wishes to produce new (non-EPI) or combination vaccines must produce some EPI vaccines (individually and not as combinations) to fill the shortfalls in Government procurement. 5) Combination of EPI and non-EPI vaccines should be banned completely, as it creates market distortions and artificial scarcity for EPI vaccines and pushes unnecessary vaccines in the name of convenient combinations at exorbitant prices.

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Brief write up of GSBPL

A Chennai based company in India. The Parent company is Green Signal.

The Company has future plans of setting up State-of-the-Art facilities for manufacturing all kinds of vaccines, namely, Tetanus Toxoid, BCG, Measles, Diphtheria, Pertussis and Rabies. It is also planning to set up R&D facilities to carry out Clinical Trials and develop new products for the Next Generation at this unit starting February 2007.

Now visualizing the Big Boom that India is poised for in the field of Bio Technology the proprietor of Green Signal has formed the private limited Company 'GSBPL' and had it incorporated in 2005 for manufacturing cost-Effective vaccines of international standards with an added intention of "Wellness for All."

Green Signal Bio Pharma Private Limited a Private Limited Company Incorporated under the Companies Act 1956 has its registered office in Chennai in the State of Tamil Nadu.

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* GSBPL plans to go into production of 0.5 million doses of Rabies vaccine (vero cell) in the first year starting September 2006 and make a 100% in the second year and a 300% increase in the third year.

* It will also venture into production of 1 million doses of Tetanus Toxoid in the first year of its inception and go on to double its production every year for the next three years

* Besides the above vaccines GSBPL also plans to produce the BCG vaccine On a larger scale of 180 million doses per annum for three years starting from Feb 2007 along with Diphtheria, Pertussis vaccine and DTAP

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Stop Press**Sacked' vaccine lab chief takes Venugopal route against Anbumani***Express News Service*

Posted online: Tuesday, May 27, 2008 at 2341 hrs

Chennai, May 26: After the AIIMS fiasco, Union Health Minister Dr Anbumani Ramadoss' attempt to shunt another top official has hit the legal blockade.

According to sources, N Elangeswaran, the former director of BCG Vaccine Laboratory, Guindy, who was relieved from the post with "immediate effect" on April 15 by the Health Ministry, has obtained a stay order from the Madras High Court. Lab officials said the director, who was on medical leave till recently, joined duty on Monday. He also sought protection from employees of the lab at a local police station.

The ministry had earlier shut down the vaccine manufacturing facility, along with two other PSU units, citing failure to keep the minimum required manufacturing practices. Elangeswaran, a former director of another vaccine manufacturing facility, the Pasteur Institute, Coonoor, was relieved from the post and later transferred to the Central Government Health Scheme as a senior specialist. However, he went on a medical leave two days after being shunted from the post.

The vaccine unit and its director was embroiled in controversy after he told a section of the media that he was being arm-twisted into stopping vaccine production at Guindy in favour of private players. He had also named two senior officials who allegedly pressurised him into agreeing to stoppage of vaccine production.

Accompanied by two police personnel, Elangeswaran resumed duty at BCG Lab on Monday morning, much to the surprise of many staff, though he refused to meet the employees' union representatives. He was not available for comment.

Govt pays crores for 'free' seeds After Rs 3.25 cr for measles seeds, Ramadoss' associate to earn Rs 143 cr

Behind the Union Health Ministry's decision to close down vaccine production by three public sector undertakings (PSUs) and purchase of measles seeds by one of them from a private company at a highly inflated cost was a well-planned conspiracy to help a politically connected small-time entrepreneur.

J. Gopikrishnan | New Delhi

The Green Signal Bio Pharma (GSBP) Limited, a Chennai-based private company, is set to walk away with Rs 143 crore over the next three years in a "joint venture" with Pasteur Institute of India, Coonoor. The PSU bought measles seeds from GSBP at a staggering Rs 3.25 crore and further agreed to give 70 per cent of the profit from vaccine manufacturing to the private company.

Investigation by *The Pioneer* has shown that the "joint venture" was forged to squarely benefit the private company, which is owned by Sundarapariipoornan, a close associate

of Union Health Minister Anbumani Ramadoss. The measles seed, a raw material for vaccine production, was available free of cost at the Indian Immunologicals (Hyderabad), another PSU. "We could have easily provided the measles seed to Pasteur Institute at bare minimum cost as it is a fellow PSU," said an official working with Indian Immunologicals.

"The other option before the Government was to source the measles seed from Serum Institute, Pune, the existing private measles vaccine producer," he said. "As the Serum Institute had received several seeds from PSUs free of cost with the concurrence of the Health Ministry, the Government could have negotiated for either free supply or persuaded them to charge nominal cost for the seed," the official said, adding, "We can't understand the role of Sundarapariipoornan. What is his credibility in supplying seeds, a critical part in vaccine production?"

The GSBP had in September 2006 bought BCG seeds from BCG Vaccine Lab, a Chennai-based PSU, for just Rs 1.05 lakh. "It is baffling that a private company buys vaccine seeds for Rs 1.05 lakh and sells another vaccine seed for Rs 3.25 crore. Also, don't forget that both the PSUs were headed by Elangeswaran," said the official. Elangeswaran had told *The Pioneer* that he was "arm-twisted" by senior officials in the Health Ministry to enter into the dubious deals.

The official said that if the seeds were not available with any recognised Indian manufacturer, the Government should have consult WHO for a list of the accredited international suppliers. The source of measles seeds is Zagreb, the capital of Croatia. Sources said that Sundarapariipoornan has not supplied any proof of supply or source of origin of the measles seed that he sold to Pasteur Institute. Scientists are not ruling out theft from Government laboratories.

The deal was signed on November 27, 2006, in utter violation of Government rules. The Pasteur Institute floated no tender and agreed to the one-sided terms as dictated by Sundarapariipoornan. The institute first proposed a 60:40 profit sharing formula, but revised it to 70:30 on GSBP's insistence.

Later, in a proposal to the Health Ministry (No. A 50011/156/2007-PIIC) on December 27, 2007, Elangeswaran sought Rs 17.80 crore for starting measles vaccine production and projected Rs 205 crore in profit over the next three years. The breakup is as follows: For 2008-09 — Rs 17.3 crore; 2009-10 — Rs 62.40 crore; 2010-11 — Rs 62.48 crore; and 2011-12 — Rs 62.55 crore.

Seventy per cent of Rs 205 crore is estimated at Rs 143 crore, the staggering amount Sundarapariipoornan is set to make for providing measles seeds to the PSU.

That the deal between GSBP and Pasteur institute was totally illegal became clear when the integrated finance division of the Health Ministry pointed out that any proposal for new activity or scheme can be taken up by an autonomous body (like Pasteur Institute) only after it was approved, in particular, by the Planning Commission and related allocation made in the Budget.

For full report see *The Pioneer* of 30th May 2008.

WHO list of vaccines for purchase by UN agencies as of May 2008

Producer	Vaccines
Berna Biotech	TT, MR (measles, rubella combination)
Berna Biotech Korea Corp.	Hepatitis B (recombinant), DTP-Hep B-Hib (fully liquid pentavalent) (Quinvaxem)
Bio Farma, Indonesia	DT, DTP, DTP-Hep B, Hepatitis B filled in Uniject, OPV, TT, TT filled in Uniject, Measles, Measles (20 doses)
Biomanguinhos, Brazil	Yellow fever (5, 10 and 50 doses) , polysaccharide meningococcal A and C vaccine (10 doses in glass vials)
Center for Genetic Engineering and Biotechnology, Cuba	Hepatitis B(recombinant)
Novartis Vaccines and Diagnostics GmbH & Co. KG, Germany (formerly Chiron Behring)	DTP, Rabies
Novartis Vaccines and Diagnostics S.r.l, India (formerly Chiron Behring)	Rabies
Novartis Vaccines and Diagnostics S.r.l, Italy (formerly Chiron Vaccines)	OPV, Hib, DTP-Hib
GlaxoSmithKline, Belgium	Hepatitis B (recombinant), Hib, OPV (produced in MRC-5), meningococcal A + C, meningococcal ACW 135; DTP-Hep B (Tritanrix) , DTP-Hep B to be combined with Hib (pentavalent) (Tritanrix-Hib) , DTP-Hep B (Zilbrix), DTP-Hep B + Hib (Zilbrix-Hib), measles, MMR, Rotavirus (Rotarix)*
Haffkine Bio Pharmaceutical Corporation Ltd, India	OPV (from bulk supplied by Biofarma, Indonesia)
Institut Pasteur Dakar, Senegal	yellow fever
Japan BCG	BCG
LG Life Sciences Ltd. , Korea	Hepatitis B (recombinant)
Merck and Co. Inc, USA	Hepatitis B (recombinant), Hib
BB-NCIPD Ltd., Bulgaria, Intervax, Canada	BCG, TT, DT, dT
Panacea Biotec, India	DTP Biofarma - Hib Novartis (1 dose) (EASYFOUR)
	DTP Biofarma - Hepatitis B PHB (1 dose) (ECOVAC)
	Hepatitis B (Enivac B)
	OPV (from bulk supplied by Biofarma, Indonesia)
	OPV (from bulk supplied from Chiron, Italy)
Sanofi Pasteur, France	DT, dT, DTP, DTP-Hib, IPV, OPV, mOPV1, TT, measles, MMR, Hib, rabies, yellow fever, meningococcal A + C
SBL Vaccin AB, Sweden	Inactivated oral cholera
Serum Institute of India	BCG, DT, dT, DTP, DTP-Hep B, Hep B (recombinant), TT, MR, MMR, measles, rubella
Shantha Biotechnics Private Ltd., India	Hepatitis B (recombinant), DTP-Hep B (Shantetra), TT (Shan TT)
Statens Seruminstitut, Denmark	BCG

Source: <http://www.who.int/immunization_standards/vaccine_quality/pq_suppliers/en/index.html>

Priorities for vaccine evaluations for prequalification for 2007-2008

Methodology used

Vaccines of interest included all vaccines currently in use by UN agencies and those in the pipeline that may become available in the coming two/three years and that are of Public Health Interest as defined by WHO, UNICEF and other partners.

Vaccines were listed and members of the two agencies independently assigned to each a level of priority ranging between 1 and 3 (3 being the highest) based on the following criteria:

- 1) demand in their respective markets
- 2) number of suppliers on the market
- 3) specific profile of the products offered

Based on the scores given by both agencies, the following priorities were established for 2007 and 2008.

High priority

- Pentavalent vaccine** (DTP-Hep B-Hib or DTP-Hep B + Hib)
- MMR group of vaccines (Measles, MR and MMR)
- Rotavirus vaccine
- Pneumococcal conjugate vaccine
- IPV and mOPV remain as priority vaccines in view of the priorities defined by the Polio Eradication Initiative.

- Seasonal Influenza vaccines

Medium priority

- Human Papilloma Vaccine
- Meningococcal A + C
- TT/Td
- Tetravalent vaccine (DTP-Hep B)**

Low priority

- Yellow Fever
- Japanese Encephalitis
- All other combinations (eg Hep B-Hib, DTP-Hib)
- DTP
- Hib monovalent
- Rabies
- Hepatitis B

** Tetravalent vaccines. In the previous biennium this vaccine was high priority and manufacturers were entitled to submit applications in parallel with the licensing process by the responsible NRA. Due to the number of tetravalent vaccines already available in the UN market, in 2007-2008 only licensed vaccine with the relevant clinical information will be accepted for prequalification evaluation. **Note: The current list may be revised within one year as required.**

Source: <http://www.who.int/immunization_standards/vaccine_quality/pq_suppliers/en/index.html>

Vaccine Manufacture Shift from Industrial to Developing Countries

- 1992, 100% of vaccine purchased by UNICEF from Industrial Nations
- 2000, 53% of vaccines purchased are from Developing Nations, which include:
- 25% of Polio, 90% of Measles, 85% of Yellow Fever, 79% of Hep. B.
- 1997-2000, 50% of Industrial Nations left BCG, DTP and TT manufacture
- 7-10 manufacturers left measles production, leaving one country supplying >90% of the UNICEF needs – risk to vaccine security.

David Wood and Lahouari Belgharbi, Quality Safety and Standards (QSS); Immunization, Vaccines and Biologicals (IVB); Family and Community Health (FCH); WHO HQ, Geneva. “Review - 10 years of strengthening vaccines regulatory capacity” presented at WHO Prequalification of Diagnostics, Medicines and Vaccines - 3rd Consultative Stakeholders Meeting. Source: <www.who.int/prequal/trainingresources/pq_pres/Stakeholders_2008/PQ_review.ppt>

Summary of the 10 year review meeting of the WHO project to strengthen vaccine regulatory capacity in countries

The World Health Organization (WHO) convened a three days informal consultation of experts from 17 to 19 December 2007 in Geneva. The meeting examined progress that has been made over the past 10 years (1997-2007) in a WHO project, managed by the Immunization, Vaccines and Biologicals Department, to strengthen vaccine regulatory capacity in countries, and to provide guidance for the future of the project. The participants were from National Regulatory Authorities (NRAs), National Control Laboratories (NCLs), national pharmacovigilance centers, and national immunization programmes representing 25 countries, all WHO regions, together with representatives from institutions such as the European Medicines Agency (EMA), the Pharmaceutical Inspection Convention/Scheme (PIC/S), and the Government of Canada.

Over the 10 year period, the vaccine regulatory system has been reviewed in 86 countries; some of these countries have had more than 10 WHO visits. More than 1 000 technical personnel have been trained through a Global Training Network (GTN), that was initiated in 1996. On the basis of this experience, a robust system of evaluation and documented methodologies to conduct an assessment of a national vaccine regulatory system has evolved, and is now available for countries to use for self-assessments. Over 400 regulatory experts have been identified to conduct assessments and a global database has been compiled for these people to serve on a roster for WHO. The impact of the vaccine NRA strengthening project has been twofold the establishment and strengthening of functional NRAs (Table) according to their respective levels of need, and a flourishing number of manufacturers particularly in the developing world capable of supplying vaccines of assured quality. The programme now supports the United Nations vaccine prequalification system. Indeed, it is a mandatory pre-condition for prequalification of a vaccine that the producing country has an assessed and functional NRA before prequalification can start.

For the future, five main themes were identified that, if addressed, will build upon the achievements outlined above, and will strengthen the project, and hence regulatory oversight of vaccines within countries. These are:

- 1) to develop a process to ensure appropriate and consistent training of newly recruited experts for the WHO assessments since the standards of the experts, and their experience and understanding of the vaccine regulatory process, inevitably vary.
- 2) to increase harmonization of the WHO assessment procedures for national regulatory oversight of vaccines and for drugs. A dual system of assessment (drug and vaccines) will create confusion amongst the NRAs and those who have to make policy decisions, and there will be fatigue, confusion and frustration amongst those reviewed. On the other hand, increased harmonization will potentially benefit

countries, simplify the process and facilitate synergies in management of both projects.

- 3) The institutional development plan (IDP) is an important and necessary outcome of the review process. It has considerable potential for increasing the capacity of individuals within the NRA and for training them. It also has bearing on improvement of systems, and within-country management. The IDP needs to contain commitment from countries regarding human resources, development of facilities, sustained financial support, political involvement and buy-in. The IDP should specify follow-up, with specific timelines, and it should be based on sound practices such as the GTN and other training activities. The IDP also places obligations on WHO to facilitate follow-up activities and more recognition of the role of the WHO Regional Offices is encouraged. For this purpose, WHO/HQ and regions should use these IDPs to a greater extent to monitor progress and coordinate support to national vaccine regulatory systems. Joint ownership of the IDP, between the country and WHO, is the best assurance for achieving sustained improvement.
- 4) There is need to continue to increase the involvement of the WHO Regional Offices in the vaccines NRA strengthening project. It is not suggested that NRA assessments for WHO vaccine prequalification purposes should be a regional activity; that is the responsibility of WHO at headquarters. However the WHO regions have much to contribute to the NRA assessment review process, especially assessments that are primarily intended for capacity building.
- 5) Vast amounts of data have been generated during the course of the project. These data are a valuable research resource, potentially for health systems strengthening research, and should be further analysed. The computerized database has an enormous potential, particularly for planning, understanding resource needs, and for developing evidence to guide policy makers.

The WHO NRA assessment process depends on the quality of its assessors and it was recommended to assess the assessors in order to sustain the system credibility. In general, the competence of the experts has been high, and their approach objective. However, there is more to be done to assure that in the future a thorough understanding of the tools and their application, and consistency between assessors are sustained. It was noted in the meeting that the WHO is not the only institution with experience in capacity building of vaccine NRAs.

Source: Extract from

<http://www.who.int/immunization/sage/2_wer_final_draft_DW_eu_rev3dw_version030308_v4.pdf>

Ghost Authorship and Ghostwriting in Publications Related to Rofecoxib

A major article has appeared in JAMA which describes a case-study of ghost authorship and ghost writing of publications related to the drug rofecoxib (Vioxx, Merck, now withdrawn from the market) that used internal company documents made public in the course of litigation about alleged injuries due to Vioxx. [Ross JS, Hill KP, Egilman DS, Krumholz HM. Ghost authorship and ghostwriting in publications related to rofecoxib: a case study of industry documents from rofecoxib litigation. JAMA 2008; 299: 1800-1812.] See also: <http://jama.ama-assn.org/cgi/content/abstract/299/15/1800?etoc>

This article should be required reading not just for anyone interested in ghost writing, but for anyone concerned about what has gone wrong with health care. The main points of the paper are:

Merck used a *systematic strategy* to facilitate the publication of *ghost authored and ghost written medical literature*. Articles related to rofecoxib were frequently authored by Merck employees but attributed first authorship to external, academically affiliated investigators who did not always disclose financial support from Merck, although financial support of the study was nearly always provided. Similarly, review articles related to rofecoxib were frequently prepared by *unacknowledged authors employed by medical publishing companies* and attributed authorship to investigators who often did not disclose financial support from Merck.

The authorship pattern observed within these documents suggests there was a *widespread practice of inappropriately attributing authorship to academic authors and a failure to disclose relevant financial relationships*.

A companion to the article on ghost writing and guest authorship, provides another vivid example of the manipulation of clinical research. [Psaty BM, Kronmal RA. Reporting mortality findings in trials of rofecoxib for Alzheimer disease or cognitive impairment: a case study based on documents from rofecoxib litigation. JAMA 2008; 299: 1813-1817.]

The article is a case-study of how mortality results of trials of rofecoxib (Vioxx, by Merck, now off the market) were reported. The article focuses on two clinical trials, 078 and 091, and compared results reported in publications, reported to the FDA, from the commercial sponsor's own analysis, and from an independent analysis of the original data done by an author of the JAMA article.

The the published reports of these trials discussed mortality thus (quoting from the JAMA article), first for study 078:

'A total of 39 deaths occurred in patients who were taking study treatment or from fatal adverse events that started within 14 days of the last dose (24 or 3.3% for rofecoxib and 15 or 2.1% for placebo). . . . There were an additional 22 deaths in the off-drug period (17 in patients assigned to rofecoxib and five in patients assigned to placebo); 12 of these (11 in the rofecoxib group and one in the placebo group) occurred more than 48 weeks after treatment discontinuation.' The report also states: 'In addition to evaluating efficacy, the present study provided important placebo-controlled data on the safety of rofecoxib 25 mg over periods of up to 4 years in an elderly population. . . . Rofecoxib was generally well tolerated by the elderly patients in the study, consistent with results from prior clinical studies in osteoarthritis (Langman et al, 1999; Reicin et al, 2002) and AD (Reines et al, 2004). The overall incidence of adverse experiences, serious adverse experiences, and discontinuations due to adverse experiences were [sic] similar or only slightly increased for rofecoxib vs placebo.' The overall impression created by this report, for which 8 of 11 authors are employees of the sponsor, is that rofecoxib was 'generally well tolerated.'

And for trial 091:

'There were no drug-related deaths during the study. Non-drug related deaths occurred in 11 patients (9 in the rofecoxib group and 2 in the placebo group) while taking study treatment or within 14 days of the last dose.' Deaths that may have occurred more than 14 days after the last dose were not reported. Regarding safety, the authors conclude that '*Rofecoxib was generally well tolerated* by the elderly patients in our study, which is consistent with results from previous clinical trials in patients with osteoarthritis.'

The reports both mention that there were more deaths in the group of patients who took rofecoxib, but did not analyze these results for statistical significance, and found no importance in these results.

Here are the results of the sponsor's own intention to treat analysis, which was done in 2001, and not sent to the FDA until 2003.

Study	Rofecoxib Mortality	Placebo Mortality	Hazard Ratio (95% CI)
091	13/346	3/346	4.43 (1.26-15.53)
078	21/723	9/732	2.55 (1.17-5.56)

Note that in both trials the death rates were statistically significantly higher for patients taking rofecoxib compared to placebo.

And the JAMA author's independent analysis of data combined from both trials showed a total mortality of 57/1069 for patients treated with rofecoxib, 29/1074 for those on placebo, and a hazard ratio of 2.13 (1.36-3.33).

Thus, it appears that the two published trial reports minimized the drug's apparent relationship to mortality by failing to do an intention-to-treat analysis, and in fact failing to do any analysis of the mortality data.

This is just the latest (but certainly one of the better publicized) examples of how commercial sponsors of clinical research may manipulate the design, implementation, analysis, and/or dissemination of results of studies to further their vested interests.

This is bad for patients because clinical decisions supposedly based on apparently the best data from clinical research may be distorted by such manipulation.

This manipulation also betrays the trust of research

subjects who volunteered to participate thinking that the results of the research were meant to further science and patient care. Instead, the manipulation of clinical research means that its results may really mainly further the marketing of the sponsors' products or services.

As the JAMA authors concluded,

The findings from this case study suggest that additional protections for human research participants, including new approaches for the conduct, oversight, and reporting of industry-sponsored trials, are necessary. A clinical trials system in which sponsors fund the trials that are conducted by independent investigators would provide additional protections.

In my humble opinion, continuing revelations about suppression and manipulation of clinical research suggest that all such research ought to be done by truly independent investigators who have no financial or other entanglements with organizations with vested interests in the research turning out a certain way.

Summarised from the posting by Roy M. Poses MD at <<http://hcrenewal.blogspot.com/search/label/manipulating%20clinical%20research>>

A Revealing Response from a Former Ghostwriter

Who actually wrote the Research Paper? How to find it out

(This is) In reply to the BMJ theme issue of 31st May 2003 (Vol 326 issue 7400) "Time to untangle doctors from drug companies."¹

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

¹ *Medical journals and pharmaceutical companies: uneasy bedfellows* in BMJ, 31st May 2003 (Vol 326, issue 7400), Richard Smith, editor, <<http://bmj.bmjournals.com/cgi/content/full/326/7400/1202>>.

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 to 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

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Competing interests: None declared

Source: Susanna T Rees, Care Assistant, BMJ, 12 June 2003. Citations in the original at <<http://bmj.bmjournals.com/cgi/eletters/326/7400/1202#33226>>

Pharma Ghost Writers¹

...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 ghostwriting research papers. Dr Richard Smith, editor of the *British Journal of Medicine*, admitted ghostwriting 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.”²

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* paper³ on the uneasy relationship between medical journals and pharmaceutical companies responded in a letter:⁴

...Last week I and my colleagues were digesting May 22, 2003 *Neuron* (a major neuroscience journal published by Cell press) article and associated editorial coverage⁵ 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 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)

¹Reproduced from (The Revised) A Layperson’s Guide to Medicines, *LOCOST, Vadodara, 2006. pp. 228 ff.*

²“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>

³“Medical journals and pharmaceutical companies: uneasy bedfellows” in *BMJ*, 31st May 2003 (Vol 326, issue 7400), Richard Smith, editor, <<http://bmj.bmjournals.com/cgi/content/full/326/7400/1202>>.

⁴Richard Smith, *op.cit.*

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Selective Publication of Antidepressant Trials: A Third of the Truth?

An even more recent paper¹ has shown that the drug companies that made antidepressants like Prozac and Paxil never published the results of about a third of the drug trials that they conducted to win government approval, misleading doctors and consumers about the drugs' true effectiveness.

In published trials, about 60 percent of people taking the drugs reported significant relief from depression, compared with roughly 40 percent of those on placebo pills. But when the less positive, unpublished trials are included, the advantage shrinks: the drugs outperform placebos, but by a modest margin, the authors conclude. Let us quote verbatim:

We obtained reviews from the Food and Drug Administration (FDA) for studies of 12 antidepressant agents involving 12,564 patients. We conducted a systematic literature search to identify matching publications. For trials that were reported in the literature, we compared the published outcomes with the FDA outcomes. We also compared the effect size derived from the published reports with the effect size derived from the entire FDA data set.

Results Among 74 FDA-registered studies, 31%, accounting for 3449 study participants, were not published. Whether and how the studies were published were associated with the study outcome. A total of 37 studies viewed by the FDA as having positive results were published; 1 study viewed as positive was not published. Studies viewed by the FDA as having negative or questionable results were, with 3 exceptions, either not published (22 studies) or published in a way that, in our opinion, conveyed a positive outcome (11 studies). According to the published literature, it appeared that 94% of the trials conducted were positive. By contrast, the FDA analysis showed that 51% were positive. Separate meta-analyses of the FDA and journal data sets showed that the increase in effect size ranged from 11 to 69%

for individual drugs and was 32% overall.

Conclusions We cannot determine whether the bias observed resulted from a failure to submit manuscripts on the part of authors and sponsors, from decisions by journal editors and reviewers not to publish, or both. Selective reporting of clinical trial results may have adverse consequences for researchers, study participants, health care professionals, and patients.

“This is a very important study for two reasons,” said Dr. Jeffrey M. Drazen, editor-in-chief of *The New England Journal* that published it. “One is that when you prescribe drugs, you want to make sure you’re working with best data possible; you wouldn’t buy a stock if you only knew a third of the truth about it.” Second, he continued, “we need to show respect for the people who enter a trial.” “They take some risk to be in the trial and then the drug company hides the data?” he asked. “That kind of thing gets us pretty passionate about this issue.”²

Admittedly, there are foundational problems like how clinical significance, efficacy, etc are defined (see box below: *Efficacy of antidepressants*). Efficacy measured in clinical trials does not necessarily translate into effectiveness in clinical practice as Turner and Rosenthal observe.³

¹Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D. Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy. *NEJM*, Volume 358:252-260 January 17, 2008 Number 3. For a more accessible report see, “Researchers Find a Bias Toward Upbeat Findings on Antidepressants” by Benedict Carey, *New York Times*, January 17, 2008.

²*New York Times*, January 17, 2008, op.cit.

³Erick H Turner, Robert Rosenthal. Efficacy of antidepressants. Editorial in *BMJ* 2008;336:516-517 (8 March). Much of the editorial is reproduced on page 17 of this issue of the *mfc bulletin*.

Efficacy of Antidepressants

Is not an absolute measure, and it depends on how clinical significance is defined

In February 2008, Kirsch and colleagues reported a meta-analysis of the efficacy of antidepressants using data from clinical trials submitted to the Food and Drug Administration.¹ They provocatively concluded, “there seems little evidence to support the prescription of antidepressant medication to any but the most severely depressed patients.”

In January this year, we published an article about the selective publication of antidepressant trials and its influence on apparent efficacy,² in which we also used FDA data. Our main finding was that antidepressant drugs are much less effective than is apparent from journal articles. From the FDA data we derived an overall effect size of 0.31. Kirsch and colleagues used FDA data from four of the 12 drugs we examined and calculated an overall effect size of 0.32.

Although these two sets of results were in excellent agreement, our interpretations of them were quite different. In contrast to Kirsch and colleagues’ conclusion that antidepressants are ineffective, we concluded that each drug was superior to placebo. The difference in our interpretations stems from Kirsch and colleagues’ use of the criteria for clinical significance recommended by the UK’s National Institute for Health and Clinical Excellence (NICE).

Clinical significance is an important concept because a clinical trial can show superiority of a drug to placebo in a way that is statistically, but not clinically, significant. Tests of statistical significance give a yes or no answer (for example, $P < 0.05$ is deemed significant, $P > 0.05$ non-significant) that tells us whether the true effect size is zero or not, but it tells us nothing about the size of the effect.³ In contrast, effect size does, and thus allows us to look at the question of clinical significance. Values of 0.2, 0.5, and 0.8 were proposed to represent small, medium, and large effects, respectively.⁴

NICE chose the “medium” value of 0.5 as a cut-off below which they deem benefit of a drug not clinically significant.⁵ This is problematic because it transforms effect size, a continuous measure, into a yes or no measure, thereby suggesting that drug efficacy is either totally present or absent, even when comparing values as close together as 0.51 and 0.49. Kirsch and colleagues compared their effect size of 0.32 to the 0.50 cut-off and concluded that the benefits of antidepressant drugs were of no clinical significance.

But on what basis did NICE adopt the 0.5 value as a cut-off? When Cohen first proposed these landmark effect size values, he wrote, “The terms ‘small’, ‘medium’, and ‘large’ are relative . . . to each other . . . the definitions are arbitrary . . . these proposed conventions were set forth throughout with much diffidence, qualifications, and invitations not to employ them if possible.” He also said, “The values chosen had no more reliable a basis than my own intuition.” Thus, it seems doubtful that he would have endorsed NICE’s use of an effect size of 0.5 as a litmus test for drug efficacy.

To illustrate Cohen’s use of “relative” with a metaphor,

imagine antidepressant efficacy measured in terms of litres of a fluid called “d-juice” (named after Cohen’s “d”—the effect size measure described here). When our group measured 0.41 litres of d-juice in the “glass” representing journal articles, but 0.31 litres in the FDA glass, we concluded that the FDA glass was empty relative to the journal glass. Nevertheless, we acknowledged that 0.31 litres was an amount that was measurable and significant. Kirsch and colleagues measured 0.32 litres of d-juice, but because they did not consider the glass sufficiently full (defined arbitrarily as $P \geq 0.5$), they concluded that the glass contained virtually no d-juice whatsoever. To summarise, we agree that the antidepressant “glass” is far from full, but we disagree that it is completely empty.

Hypothetically, if antidepressants are not worth taking, then what should doctors and patients do? Kirsch and colleagues recommend that if antidepressants are to be used at all they should be used only when alternative treatments have failed to provide a benefit.¹ Although the authors did not specify a preferred first line treatment, they may have had psychotherapy in mind.^{6,7} It seems unfair that pharmacological, and not psychotherapeutic, treatment has become the usual first line approach to depression merely for economic reasons.² But before we embrace any treatment as first line, it is prudent to ask whether its efficacy is beyond question. For psychotherapy trials, there is no equivalent of the FDA whose records we can examine, so how can we be sure that selective publication is not occurring here as well?

Our clinical recommendation is that when considering the potential benefits of treatment with antidepressants, be circumspect but not dismissive. Efficacy measured in clinical trials does not necessarily translate into effectiveness in clinical practice.⁸ Patients’ individual responses are like clinical trial effect sizes in that they are not all or none. Thus, when a patient is tried on his or her first antidepressant, a partial response should not be surprising or discouraging. Also, depression rating scales used in clinical trials seldom measure quality of life, which has been suggested to be a reasonable measure of clinical significance.⁹

With regard to policy, we reiterate our request in 2004 for drug regulatory authorities such as the FDA to make their reviews publicly available on the world wide web—retrospectively.¹⁰ Making this unbiased information more accessible will allow other researchers to move beyond antidepressants and ascertain the true efficacy of all marketed drugs.

Erick H Turner, *assistant professor*¹, Robert Rosenthal, *distinguished professor*²

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References in the original BMJ Editorial. 2008;336:516-517 (8th March). Reproduced in public interest.

Patrick Geddes: People's Architect

"FOR A LONG PERIOD, MUNICIPALITIES HAVE neglected their poorer quarters and these have become ever more unsanitary and congested.

When the position grows quite intolerable some piecemeal sanitary improvements are undertaken. These must be maintained, and inspections and inspectors multiply. Sooner or later the inadequacy of those methods is realized and it is decided that 'something must be done'. The Municipality moves from these weak and critical methods to the opposite extreme of sweeping demolition. The effect of the demolitions is to increase overcrowding in the surrounding areas, heighten the rents and intensify the poverty of the population. The well-meaning Municipality next sets about vast schemes of water-supply and drainage, which are sometimes questionable and sometimes unsuccessful but always very costly. Often these also involve sweeping destruction of old wells and reservoirs and too often all ordinary drainage repairs are held up until the new drainage is ready. This provides the unfortunate and impoverished citizens with a further term of years of increased deterioration and unremoved dirt.

The whole process becomes increasingly expensive and Government doles are often sought; and wasted when given."

If you think these observations are from a leftist from a third world country – you are wrong. These observations are from the pen of Patrick Geddes an English architect who was in India between 1915 and 1919. That was the time when the British Imperialism was at its height. Congress party became a peoples' party only in 1920s. Not only was the average Englishman convinced of the superiority of his ideas and outlook and looked down upon the Indian tradition, but the Indian experts who were imitating the British were also convinced that the English culture, architecture, town planning, etc., were the best in the world and had a contemptuous attitude towards everything Indian.

In such a situation, Patrick Geddes showed great sympathy for the religions and social practices of the local communities and came up with town planning projects for some forty Indian cities, people friendly, economical, eco friendly and aesthetic. In an introduction to Patrick Geddes' work written in 1946, Lewis Mumford, an ecologist par excellence, observes "Geddes was far in advance of his generation. His planning challenged the idols of officialdom; it was conceived in terms of primary human needs... To use town planner's art, Geddes brought the rural virtues: not merely respect for the land and for agricultural processes; but the

patience of the peasant, and the sense that orderly growth is more important than order at the expense of the growth." Advocates of Special Economic Zones for Nandigram and other places, please take note.

In Geddes's words, "**Town-planning is not mere town planning, not even work planning. If it is to be successful it must be folk planning.**"

When Europeans first settled in India they found conditions in the cities so unhealthy, noisy, and otherwise distasteful, that they started independent colonies outside - 'cantonments' for the military and 'civil lines' for officials and businessmen. They did not care for the local population. Later on, when town planning started for the locals, it was the European model. In such a situation, Geddes struck a different note.

Geddes advocates tree planting – especially fruit-yielding trees and vegetable gardens as integral to town planning. "I insist that an enormous proportion of the diseases of children - and of men and women - would disappear if there were a substantial increase of fresh vegetables and fruits in their diet. Further, everyone knows that the most destructive of the diseases of India are diseases of the alimentary canal and that these diseases are communicated in two ways, by dust and by polluted water. These planting proposals would greatly diminish both the dispersal of dust and the pollution of water.

Such observations and details form part of the book. Shri Ramachandra Guha in his foreword to the 2007 edition of the book finds three central themes in Geddes work. First is 'Respect for Nature'. His approach is deeply ecological emphasising a city's relationship to its water resources the promotion of parks and trees, the importance of recycling, and the lessening of dependence on the resources of the hinterland. The second theme is 'Respect for Democracy'. He insisted that the residents of a city must help design plans made for them. The third theme is 'Respect for tradition, appreciation of all that is best in the old domestic architecture of Indian cities and of renewing this when it has fallen away.'

There are 24 pages of beautiful black and white photographs on art paper and some drawings which have great historic value rendering this book a collector's item.

The title of the book is *Patrick Geddes in India*, first published in 1947. The 2007 edition has been published by Select books, 71 Brigade Road Cross, Bangalore 560 001. selectbooks@hotmail.com – Editorial coordination Subbakrishna Rao, Suma Ponnamma.

CRPF Men Gun Down Child, Woman in Chhattisgarh Camp

Indo-Asian News Service

RAIPUR, May 23: A child and a woman were killed instantly when dozens of Central Reserve Police Force (CRPF) troopers lined up men and women and fired at them in a village deep in Chhattisgarh's forested Bijapur district, which is a Maoist hot-bed, official sources said today.

Raju, 2, and Ram Bai, 25, died on the spot in the CRPF troopers' gunfire. A six-year old boy and a woman were critically injured when the CRPF men posted at Cherpal village allegedly assaulted the tribals. The injured have been rushed to the district hospital at Bijapur. Bijapur district Superintendent of Police Mr Ankit Garg said: "We are probing into the circumstances that provoked gunfire, killing two persons." Cherpal, located some 450 km south of here, is one of the villages where about 1,200 tribal persons were uprooted due to a civil militia movement, Salwa Judum, launched in June 2005 against the Maoist

insurgents. They are now settled in a government-run makeshift relief camp.

Official sources say that CRPF troopers deployed at the relief camp to guard them against Maoists, asked the men and women at midnight to come out for an urgent meeting and then started beating them up. Tension gripped the entire area after camp settlers raised slogans today and assembled in hundreds outside the district hospital to protest against the incident. The police have registered a case and have begun a probe.

The camp settlers claim that trouble began when a few CRPF troopers tried to molest some tribal women and met with resistance. Senior police officers at the police headquarters are not forthcoming. An officer said: "We are collecting details of the shocking incident."

<<http://www.thestatesman.net/> >

PIL filed

MFC and Others Implead in Madras HC for Vacating Stay

MFC, AIDAN, LOCOST, DAF-K and CONCERT Chennai have filed a PIL in the Chennai High Court during April 2008 asking for vacating the stay given to Confederation of Indian Pharmaceutical Industry (SSI) and some other pharma manufacturers. The stay was given by the Madras HC on the Drug Controller's order to withdraw a list of 300 and more FDCs (Fixed Dose Combinations).

The petition of MFC et al pointed out that although the list of the DCGI was not exhaustive, and perhaps even a half-baked job, it was a move in the right direction and hence giving stay will violative of justice and the public at large will be put to severe loss and hardship.

The petition quotes inter alia WHO sources as saying: Most essential medicines should be formulated as single compounds. Fixed-dose combination products should be selected only when the combination has a proven advantage in therapeutic effect, safety, adherence or in decreasing the emergence of drug resistance in malaria, tuberculosis and HIV/AIDS." [Source: WHO Expert Committee on the Selection and Use of Essential Medicines (12th: 2002: Geneva, Switzerland). The selection and use of essential medicines: report of the WHO Expert Committee, 2002: (including the 12th

model list of essential medicines). (WHO technical report series; 914). Also in: WHO Expert Committee on the Selection and Use of Essential Medicines (14th: 2005: Geneva, Switzerland). The selection and use of essential medicines: report of the WHO Expert Committee, 2005: (including the 14th model list of essential medicines). (WHO technical report series; 933), page 57.]

A WHO manual for drug regulatory authorities has the following to state about FDC's:

"New fixed-ratio combination products are regarded as new drugs in their own right. They are acceptable only when (a) the dosage of each ingredient meets the requirements of a defined population group, and (b) the combination has a proven advantage over single compounds administered separately in terms of therapeutic effect, safety or compliance. They should not be treated as generic versions.

[World Health Organization. Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (generic) Products: A Manual for a Drug Regulatory Authority. WHO/DMP/RGS/98.5 (1998)]. The complete petition is available at the mfc website, <www.mfcindia.org>.

MFC Mid-Annual Meeting

The next mid annual meeting of the Medico Friend Circle is scheduled for July 4 and 5, 2008 at Yatri Niwas, Sewagram. The meeting will start at 10 am on the 4th and it is hoped that it will end by 4 pm on the 5th afternoon.

The main purpose of this meeting will be planning for the annual meet in December. As discussed and decided at the Dalli Rajhara meeting in Dec 2007, the theme of the January 2009 annual meet is "Health and Displacement".

The venue of the annual meet will be either in Guwahati or Bonagaigaon, or somewhere else in the North East, and the dates for that will be Jan 9 to 11, 2009. The theme assumes special significance for the North east as they many there have suffered disproportionately higher ill consequences of displacement in Independent India.

It will be desirable that those of us who feel concerned about this theme attend this meet in order to develop the discussions better. Further, the MAM will be an opportunity for us to inform ourselves and confer on other issues that concern MFC presently - such as continued incarceration of Binayak Sen and the vaccine issue.

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