IN THE SUPREME COURT OF INDIA

WRIT PETITION 79 OF 2012

Anand Rai …Petitioners

Versus

State of Madhya Pradesh …Respondents

ADDITIONAL AFFIDAVIT ON BEHALF OF THE PETITIONER

I, Dr. Anand Rai S/o Sri Awadh Narayan Rai, aged 35 years, resident of 118, Radio Colony, Residency Area, Indore, M.P. do hereby state as under:

1. **I am making this affidavit to put on record a critique of the Prof. Ranjit Roy Chaudhury Expert Committee to Formulate Policy and Guidelines for Approval of New Drugs, Clinical Trials and Banning of Drugs (hereinafter report**) which I have prepared on the basis of inputs given to me by a range of experts. I am also making a critique of the notifications dated 30.1.03 [G.S.R. 53(E)], 1.2.13 [GSR 63(E)] and 8.2.13 [GSR 72 (E)] issued by the Union of India during the progress of this case.

2. It is necessary at the outset to clarify certain basic terms which will be used both in the report and the critique. It is first of all important to understand what is meant by new chemical entities (NCEs) and Phase I - Phase IV clinical trials. New chemical entities

(NCEs) or new molecular entities (NMEs) are experimental drugs which are not approved for use in humans by any regulatory agency in the developed world or in countries having a strict regulatory system, because the safety and efficacy has not been established and these substances pose a serious risk to patients anywhere.

3. Phase I – Phase IV clinical trials are defined in the "Ethical Guidelines for Biomedical Research on Human Participants" of the Indian Council of Medical Research, New Delhi, 2006 (hereinafter ICMR Guidelines) and are as under:

Phase I (Human Pharmacology): This is a non-therapeutic trial and the objective is to determine the safety of a new drug and determine the **maximum tolerated dose** as also to determine the nature of adverse reactions that can be expected. In **healthy adults** of both sexes. Healthy female volunteers could be included provided they have completed their family or do not intend to have a child in the future. These studies include both single and multiple dose administration and should ideally be carried out at a site that is adequately equipped. The following points should be considered before initiating the trial :

a. At least two participants should be administered each dose to establish the safe dose range **using maximum tolerated dose,** pharmacokinetic, pharmacodynamics effects, and adverse reactions, if any, with their intensity and nature.

b. As this involves testing in humans for the first time, it is safer to plan the study in cohorts of volunteers by starting from the lowest dose, which is increased to higher doses only after the safety of the lower doses is clearly established.

c. Early measurement of drug activity as preliminary study of activity of potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later Phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage. This also can be carried on patients if the drug has cytotoxic potential as in case of cancer or if quicker results are needed as in case of HIV.

d. Pharmacokinetics i.e. characterization of a drug's absorption, distribution, metabolism and excretion (ADME), should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations. Obtaining pharmacokinetic information in sub-populations such as patients with impaired elimination (renal or hepatic failure), the elderly, children, and ethnic subgroups should also be considered.

e) Pharmacodynamics: Depending on the drug and the endpoints studied, pharmacodynamic studies which relate to blood levels of drug to response (pharmacokinetic/ pharmacodynamic studies) may be conducted in healthy volunteers or in patients with the

target disease. Such data obtained from patients may guide the dosage and dose regimen to be applied in later studies.

f) Investigator trained in clinical pharmacology should preferably carry out these studies.

g) The duration of time lapsing between two trials in the same volunteer should be a minimum of 3 months. The volunteers should preferably be covered under some insurance scheme.

h) Compensation is given by the sponsors of newly developed drugs. The amount may vary depending upon the discomfort experienced by the participant and the number of samples taken or being subjected to procedures. The EC has to examine this does not tantamount to undue inducement.

i) There should be adequate safeguards for management of **adverse reactions, including resuscitative measures as in intensive care.**

Combined Phase I and Phase II - Such trials are conducted on populations for whom the therapeutic options are exhausted, as in the case of HIV/AIDS and cancer. Toxic drugs like anti-retroviral or anti-cancer drug, cannot be tested in normal healthy volunteers as in Phase I studies as the risk far outweighs any benefit. Hence such studies are planned in patients suffering from the disease so that the risk benefit ratio is more favorable. Since here the patient population is a vulnerable group and trial on them has to be

planned very carefully. The role of ethics committee assumes great importance here as the weighing of the risk-benefit ratio influences the decision and participation in terminal stages may be considered to be inducement. The researcher also has to consider very carefully the risks involved.

Phase II (Therapeutic Exploratory Trials) - These are controlled studies conducted in a limited number of patients of either sex to determine therapeutic effects, effective dose range and further evaluation of safety and pharmacokinetics in patients. Generally due to selection of patients with narrow inclusion criteria to find effective dose the study population is more or less homogenous. The **dose used is lesser than the highest dose used** in phase I. Another objective of this Phase II is evaluation of potential study endpoints, therapeutic regimens including concomitant medications and target populations, and mild versus severe disease, for further studies in Phase II or III. These objectives may be served by exploratory analyses of subsets of data and by including multiple endpoints in trials. Normally 20 - 25 patients should be studied for assessment of each dosage. These studies are usually limited to 3 - 4 centres. It is advisable to include a clinical pharmacologist as a co-investigator in such studies.

Phase III (Therapeutic Confirmatory Trials) – The purpose of these trials is to obtain adequate data about the efficacy and safety of drugs in a larger number of patients of either sex in multiple centres usually in comparison with a standard drug and / or a

placebo if a standard drug does not exist for the disease under study. This is to validate efficacy and safety found in Phase II. On successful completion of phase III trials permission is granted for marketing of the drug.

Studies in Phase III may also further explore the dose-response relationship to drug concentration in blood and clinical response, use of the drug in wider populations, in different stage of disease, or the safety and efficacy of the drug in combination with other drug (s). For drugs intended to be administered for long periods, trial involving extended exposure to the drug are ordinarily conducted, although they may be initiated in Phase II. These studies carried out in Phase III complete the prescribing information needed to support adequate instructions for use of the drug.

These trials may be carried out by clinicians in the concerned therapeutic areas having facilities appropriate to the protocol. If the drug is already approved/ marketed in other countries, Phase III data should generally be obtained in sufficient numbers of patients distributed over adequate number of centers, primarily to confirm the efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information. Open non-comparative trials do not generate any generalizable data and therefore, are unethical. Studies in Phase III may also further explore the dose-response relationships, drug concentration in blood and clinical response, use of the drug in wider population, in

different stage of disease, or the safety and efficacy of the drug in combination with other drugs.

Phase IV - The Phase IV studies should have valid scientific objectives. After approval of the drug for marketing, phase IV studies or **post marketing surveillance** is undertaken to obtain additional information about the risks and benefits resulting from long term usage of drug. It is an important aspect of drug trial on the long term effects of the drugs and the **adverse reactions induced by drugs**, if any, should be brought to the notice of the Ethics Committee. There is a need to correlate the adverse events reported during Phase IV trials with the toxicity data generated in animals, to draw markers for future warnings of potential adverse events likely to occur with other drugs These trials may not be necessary for approval of new drug for marketing but may be required by the Licensing Authority for optimizing its use. These studies also include those on specific pharmacologic effect, drug-drug interaction(s), dose-response studies, trials designed to support use under approved indication(s) e.g. mortality/morbidity studies, clinical trials in a patient population not adequately studied in the pre-marketing phase, e.g., children; and epidemiological studies etc. Bioequivalence and bioavailabilty study also falls under this category. In addition there are Phase IV studies that are designed to evaluate the marketed drug in specifically designed studies, which have inclusion/exclusion criteria, objectives and end points. The drug is used for the labeled indication in these studies.

Therefore Licensing Authority permission is not needed. However, EC permission is needed.

A third type of post-marketing study involves evaluation of the drug for a new indication of a marketed drug, eg. Studies with letrazole. Here, DCGI permission and EC approval are needed which really makes the trial a Phase III study.

4. Phase I trials on new chemical entities (NCEs)/investigational new drugs on healthy human volunteers have never been permitted in India and correctly so since they are very risky and these drugs have only been evaluated with respect to laboratory animals and animal data. These Phase I trials are generally carried out in developed countries under very strict safety regimes. Since India has very lax and corrupt systems it is not advisable that the long standing policy with regard to Phase I trials be changed.

5. The above prohibition, however, does not apply for new drug substances discovered in India. This exception is set out in clause 1(1)(iv)(a) of Schedule Y of the Drugs and Cosmetic Rules, 1945, which is as under:

> "(a) for new drug substances discovered in India, clinical trials are required to be carried out in India right from Phase I and data should be submitted as required under Items 1, 2, 3, 4, 5 (data, if any, from other countries) and 9 of Appendix I."

6. Therefore, there is nothing in a law which prevents a domestically discovered drug from being tested in India from the Phase I trial stage. This submission, however, is more of an academic point as Indian companies have not discovered a single drug domestically which is recognized globally.

7. Back door entry of Phase I trials for NCEs/NMEs is introduced by the Committee in the following sly fashion:

> "For all NCEs/NMEs developed outside India which are of relevance to our population, it is not always necessary to carry out Phase I trials in our country, provided Phase I trials have either been done or are being done in the country of origin.
>
> All NCEs/NMEs undergoing clinical trials anywhere can also undergo parallel Phase II and Phase III trials in India, after carrying out a safety assessment through Phase I trials. The Phase I trials should have been done in the country of origin if the disease is prevalent there."

8. Prior to January 2005, Phase II trials of NCEs discovered/patented abroad which were not approved for use in humans in other countries were not carried out in India because these trials were risky and required very strict supervision and control. After January 2005, such trials were permitted. No reasons were given for

changing the rules. Nor has any information been published on the effect of such change in the rules.

59th Parliamentary Committee Report

9. Phase III trials of NCEs/NMEs are permissible in India. However, these trials were conducted in an utterly disgraceful manner necessitating the setting up of a Department Related Parliamentary Standing Committee on Health and Family Welfare (Rajya Sabha) which made the 59th Report on the Functioning of the Central Drugs Standard Control Organisation (CDSCO) dated 8.5.12. (See pages 535 onwards)

10. In its 59th Report the Committee "expresses its deep concern, extreme displeasure and disappointment at the state of affairs" and recommended that "all the cases…should be investigated and responsibility fixed and action taken against erring officers whether currently in service or retired". Accordingly the Committee made recommendations which are to be found from page 566 onwards Vol. II and directions are sought from this Court in line with those recommendations.

11. A summary of the recommendations abovementioned are given herein below:

    a) Phase III trials ought to be broad based and spread across the country and conducted in well equipped medical colleges and large hospitals with round the clock

emergency services to handle serious side effects, and not in private clinics. (Para 7.28, 7.29). The 330 teaching medical colleges in the country should be used for this purpose.

b) For an order directing the DCGI (Petitioner suggests CBI) to conduct an investigation into the illegal approval of drugs as set out in paragraphs 7.14 onwards.

c) For an order directing MCI to conduct an investigation and take action in accordance with law in respect of the role of doctors in the grant of illegal approvals as set out in the 59th Report.

d) For an order directing the CDSCO to choose experts in accordance with the recommendations of the 59th Report and to insist that all experts file a conflict of interest declaration as set out in the report.

e) For an order setting aside the DCGI approvals granted illegally for the drugs as set out in the 59th Report and for the constituting of an independent committee of experts to re-examine all the cases of illegal drug approvals as set out in the 59th Report.

f) All licenses granted for fixed dose combinations without prior approval should be banned under section 26 A of the Drugs and Cosmetics Act.

g) The CDSCO should put in place an effective system for controlled post marketing Phase IV studies for a large number of persons to collect information about adverse effects on patients in India.

66th Parliamentary Committee Report

I.A. 3 page 1 onwards

12. After the publication of the 59th Report on 7.8.12, Government of India submitted its Action Taken Note (ATN) on 12.9.12. The Committee examined the replies and found "most of them were **evasive, inconclusive, dilatory and vague**…without any firm commitment about the implementation of the recommendations…The Ministry…continues to be in a state of **profound procrastination**…This almost borders on **collusion** with an intension to save the guilty…there is no scientific evidence to show that these 33 drugs approved in the period January 2008 to October 2010 are really effective and safe in Indian patients…Ministry has chosen to take no action to resolve it even after a lapse of more than 7 months… The Committee takes strong objection to these dilatory tactics...**Trials should be conducted in well equipped medical colleges and large hospitals with round the clock emergency services to handle unexpected serious side effects and with expertise in research and not in private clinics...**"(page 68 IA 3)…There is adequate documentary evidence to come to the conclusion that **many**

opinions were actually written by the invisible hands of drug manufacturers and experts merely obliged by putting their signatures…The Committee is **aghast** to note the paralytic inertia gripping the Ministry…It has neither the intension to clean the augean stables of CDSCO nor any concern for probity or rule of law…"

72nd Parliamentary Committee Report (30.8.13)

I.A. 4

13. During March, 2010 the entire world was shocked by the media reports about the deaths of some female children and adolescents in Khammam district of Andhra Pradesh after being administered Human Papilloma Virus (HPV) vaccines. The vaccination trials were carried out by an American agency viz. Programme for Appropriate Technology in Health (PATH). The project was reportedly funded by Bill and Melinda Gates Foundation, an American charity. It was admitted by the Secretary that the DCGI guidelines were not adhered to.

14. A clinical trial under the title 'Post-licensure observational study of Human Papilloma Virus Vaccination – Demonstration Project' was undertaken by Programme for Appropriate Technology in Health (PATH), an agency of American origin. The Indian Council of Medical Research (ICMR), which is the highest body in the Country for medical research and related matters lent its platform to PATH in an improper and unlawful manner. The State Governments of Andhra Pradesh and Gujarat swayed by the involvement of ICMR followed suit.

15. The Committee finds the entire matter very intriguing and fishy. The choice of countries and population groups; the monopolistic nature,

at that point of time, of the product being pushed; the unlimited market potential and opportunities in the universal immunization progammes of the respective countries are all pointers to a well planned scheme to commercially exploit a situation. Had PATH been successful in getting the HPV vaccine included in the universal immunization programme of the concerned countries, this would have generated windfall profit for the manufacturer(s) by way of automatic sale, year after year, without any promotional or marketing expenses. It is well known that once introduced into the immunization programme it becomes politically impossible to stop any vaccination. To achieve this end effortlessly without going through the arduous and strictly regulated route of clinical trials, PATH resorted to an element of subterfuge by calling the clinical trials as "Observational Studies" or "Demonstration Project" and various such expressions. Thus, the interest, safety and well being of subjects were completely jeopardized by PATH by using self-determined and self servicing nomenclature which is not only highly deplorable but a serious breach of law of the land.

16. The Committee is unable to understand as to how ICMR could commit itself to support "the use of the HPV vaccine" in an MOU signed in the year 2007 even before the vaccine was a p r o v e d for use in the country, which actually happened in 2008. The Committee also questions the decision of ICMR to commit itself to promote the drug for inclusion in the Universal Immunization Programme (UIP) even before any independent study about its utility and rationale of inclusion in UIP was undertaken.

17. The Committee feels that there was serious dereliction of duty by many of the Institutions and individuals involved. The Committee

observes that ICMR representatives, instead of ensuring highest levels of ethical standards in research studies, apparently acted at the behest of the PATH in promoting the interests of manufacturers of the HPV Vaccine. It was unwise on the part of ICMR to go in the PPP mode with PATH, as such an involvement gives rise to grave Conflict of Interest. The Committee takes a serious view of the role of ICMR in the entire episode and is constrained to observe that ICMR should have been more responsible in the matter. The Committee strongly recommends that the Ministry may review the acti vi ti es of ICMR functionaries involved in PATH project.

18. The Committee from its examination has found that DHR/ICMR have completely failed to perform their mandated role and responsibility as the apex body for medical research in the Country. Rather, in their over-enthusiasm to act as a willing facilitator to the machinations of PATH they have even transgressed into the domain of other bodies/agencies which deserves the strongest condemnation and strictest action against them. The Committee fails to understand as to why ICMR took so much interest and initiative in this project when the safety, efficacy and introduction of vaccines in India is handled by National Technical Advisory Group on Immunization (NTAGI). The submissions of the Secretary, DHR/DG, ICMR before the Committee about the commencement of the project, facts of the case and the action taken have also failed to stand scrutiny during the Committee's examination of the matter. The Committee, therefore, reiterates the recommendation made in their Forty- first Report that the matter of allowing trial of the vaccine as also the approval for its marketing in the Country be inquired into by a premier investigating agency and appropriate action be taken thereafter by the Government in the matter.

The Committee expects the Government not to procrastinate in this matter any further.

19. The Committee's examination has proved that DCGI has also played a very questionable role in the entire matter. Initially, it took a call that since human subjects, as part of the studies, were receiving invasive intervention like immunization, clinical trial rules must be enforced. However, it remained as a silent spectator thereafter, even when its own rules and regulations were being so fragrantly violated. The approvals of clinical trials, marketing approval and import licenses by DCGI appear to be irregular. Therefore, the role of DCGI in this entire matter should also be inquired into.

20. In order to verify the Ministry's claim, the Committee picked just one member i.e., Professor and HoD of the Department of Obstetrics and Gynaecology (O&G) of All India Institute of Medical Sciences (AIIMS). It was found that manufacturers of Gardasil, Merck was sponsoring and funding a trial in the Department of O&G at AIIMS to determine if 2 doses of Gardasil can be used safely and effectively instead of 3 doses. Documents received by the Committee in connection with the examination of AIIMS also revealed that the individual in question availed the hospitality of these very sponsors during the said individual's visit to Seoul to attend a conference. The FCRA application form was, therefore, deliberately left incomplete to hide this truth. All these speak of a serious conflict of interest of this member of the Inquiry Committee.

21. The Committee notes that once this matter was taken up by it, the Government appointed an Inquiry Committee on 15 April, 2010 to inquire into 'alleged irregularities in the conduct of the studies using HPV

vaccines by PATH in India'. The Committee has noted the serious conflict of interest of members of this Inquiry Committee with the subject matter. The Committee, therefore, strongly deprecates the Government for appointing a committee to inquire into such a serious matter in such a casual manner even without ascertaining as to whether any of the members of the said Inquiry Committee were having any conflict of interest with the subject matter of inquiry. The Committee finds it very intriguing as to when the Inquiry Committee after having sought details of some core issues in the very first meeting of the Committee on 21 April, 2007 subsequently chose not to pursue them purportedly because 'it wanted to restrict itself to its terms of reference'. These core issues raised by the Inquiry Committee earlier, if pursued to their logical end, would not only have provided the Inquiry Committee a lot more clarity in unraveling the truth but also the Country would have known the exact details as to what transpired in this sordid incident.

22. Obtaining Informed Consent from study subjects is a core requirement in the conduct of clinical trials and protection of human rights. In case of minors, the Consent has to be signed by parents/guardians. In the case of uneducated signatories, an independent person has to explain and witness the consent process. The Informed Consent document approved by various Ethics Committees on PATH project included the sentence: "I have read the information in this consent form (or it has been read to me). I consent to allow my daughter to receive three doses of HPV vaccines." In the case of Andhra Pradesh 9,543 forms were signed, 1,948 had thumb impressions while hostel warden had signed 2,763 forms. In the case of Gujarat 6,217 forms were signed, 3,944 had thumb impressions and 545 were either signed or carried thumb impression of guardians. The data shows that a

very large number of parents/guardians were illiterate and could not even sign in their local language i.e. Telugu or Gujarati.

23. One of the experts, while going into the question of Informed consent in great detail, in two reports, has pointed out glaring discrepancies. Out of 100 consent forms for AP Project taken for study, it was found that signatures of witnesses were missing in 69 forms. In many forms there were no dates while in others the signature of just one person appeared in seven forms The legality of the Andhra Pradesh State Government circular directing all Headmasters/Wardens in all private/government /ashram schools to sign the consent forms on behalf of parents / guardians was also questionable.

24. The Committee observes that obtaining informed consent from study subjects is a fundamental requirement in the conduct of clinical trials to ensure that the human rights of the study subjects are ensured. In case of minors it is mandatory that the consent be signed by parents/guardians. For the uneducated subjects, the law requires an independent person to explain and witness the consent process. The Committee is however, deeply shocked to find that in Andhra Pradesh out of the 9543 forms, 1948 forms have thumb impressions while hostel wardens have signed 2763 forms. In Gujarat, out of the 6217 forms 3944 have thumb impressions and 5454 either signed or carried thumb impressions of guardians. The data also revealed that a very large number of parents/guardians are illiterate and could not even write in their local languages viz. Telugu or Gujarati. The Committee is further shocked to find from one of the reports that out of 100 consent forms for Andhra Pradesh project signatures of witnesses were missing in 69 forms. In many forms there were no dates. One particular person had

signed seven forms. In fact the legality of Andhra Pradesh State Government directing headmasters in all private/Government /ashram/schools to sign the consent form on behalf of parents/ guardians is highly questionable. The absence of photographs of parents/guardians/wardens on consent forms, the absence of signatures of investigators; the signatures of parents/ guardians not matching with their names; the date of vaccination being much earlier than the date of signature of parents/guardian in the consent forms, etc. all speak of grave irregularities. The Committee, accordingly, concludes that most, if not all consent forms, were carelessly filled-up and were incomplete and inaccurate. The full explanation, role, usefulness and pros and cons of vaccination had not been properly communicated to the parents/ guardians. The Committee observes that there is a gross violation of the concept and legal requirement of consent which had been substantiated by the experts. The Committee takes a serious view of the violations and strongly recommends that on the basis of the above facts, PATH should be made accountable and the Ministry should take appropriate action in the matter including taking legal action against it for breach of various laws of the land and possible violations of laws of the Country of its origin.

25. The Committee, in the light of the observations made by experts, feels that the methodology and implementation of the study at both the places was full of flaws. The Committee is of the view that since the population under study was vulnerable, utmost caution should have been exercised in the implementation of the study. The Committee also recommends that there should be an independent monitoring mechanism in such a study involving human participants so that the accurate recording of AEs and SAEs could be made. The findings of the

experts clearly indicate that the safety and rights of the children in this vaccination project were highly compromised and violated. The Committee is also concerned over the fact that there was no insurance cover for the children. The Committee strongly recommends that while allowing any such trial in future, all the lapses pointed out by the experts should be addressed effectively. ICMR and DCGI should ensure strict adherence to the guidelines, methodology and monitoring.

26. The Committee takes a serious note of the fact that both the Ethics Committees existed only as a formality and they did not play the role they were designated for. This is a clear dereliction of duty on the part of the Ethics Committees. The Committee apart from recommending suitable action in the matter, strongly recommends that there should be a mechanism in place to take appropriate action against such dereliction of duty on the part of the Ethics Committees. There should be specific guidelines for Ethics Committees and the Ethics Committees should strictly follow them. The functioning of Ethics Committees should be regularly monitored.

27. The Committee observes that the wrongful use of the NRHM logo for a project implemented by a private, foreign agency as well as the identification of this project with the U I P has adversely affected and damaged the credibility of the programme as well as that of the NRHM. The Committee, therefore, recommends that such practices of diverting public funds for advancing interests of a private agency should never be allowed in future. The Committee strongly recommends that strict action should be taken against those officials responsible for such lapses.

28. Considering the above lapses and irregularities committed by PATH during the course of conducting the trials on hapless tribal children

in Andhra Pradesh and Gujarat, the Committee is convinced that the authorities concerned did not exercise due diligence in scrutinizing the publicity material of PATH. Blurring the distinction between the UIP and PATH project due to the involvement of the State Governments in the project and ignoring the financial contribution of ICMR and the State Governments are very serious issues. The Committee, therefore, recommends that the Ministry should investigate into the above acts of omissions and commissions and take necessary action against those who are found responsible for breach of rules and regulations.

29. The Committee is amazed at the audacity of DCGI to merely repeat various steps which it proposes to take as if they are new, additional measures. All these are already part of the written rules and are supposed to be followed by all sponsors. Except for slight amendment in the Informed Consent Form, there is nothing new in the ATN submitted by DCGI. The Committee not being convinced with the action taken by the Department or DCGI, feels that the whole issue has been diluted and no accountability has been fixed on the erring Officials /Departments for the gross violations committed in the conduct of Study. The Committee also feels that a very casual approach has been taken by the Department in the matter and their replies lack any concrete action to protect and safeguard the health of our people. The Committee also noticed lack of firm action on the part of DCGI, to avoid such irregularities in future. One of the actions proposed by the DCGI to check any recurrence of such gross violations was 'proposal to amend the definition of New Drug during the next meeting'. The same assurance was given by DCGI in December, 2012. The Committee, accordingly, observes that response of the Department and DCGI is very

casual, bureaucratic and lacks any sense of urgency. The Committee feels that DCGI is not very serious in bringing improvements in the system. It, therefore, desires the Ministry to ensure compliance by DCGI.

30. The Committee is concerned that if PATH can set up an office in India so easily without getting the required mandatory approvals/ permissions, then individuals and entities inimical to the interest of the country can do the same. The Committee expresses its concern that paper and shell companies can be easily registered in many jurisdictions and then set up a place of business in India as "Liaison offices" with no questions being asked. It is surprising that security and intelligence agencies did not raise an eyebrow on the way a foreign entity entered India virtually incognito through the backdoor. The Committee desires that such incidents should not be allowed in future. The Government should tighten the rules lest one day foreign citizens, with deep roots in organizations/nations inimical to India, set up offices in the country to engage in anti-national and/or unlawful activities. It is apparent the PATH has exploited with impunity the loopholes in our system as also the absence of a nodal point or a single window for maintaining a data bank of foreign entities entering the Country for setting up their offices. Given the multiplicity of agencies involved in processing such requests there is a definite need for a nodal agency which would keep a tab on all such existing and aspiring agencies from the point of view of having obtained all necessary clearances/ permissions before commencing their operations in India. The Committee strongly recommends that government set up one such umbrella agency which should be linked to all the agencies that are involved in processing such requests. The Committee desires that within three months such an agency should be put in place and start functioning. The proposed nodal agency should

be a part of MHA with a well established coordination mechanism with the MEA so that undeserving cases are dealt forthwith through diplomatic channels. All ministries/departments /agencies/state governments/other entities should be required to share details of all requests/proposals from foreign entities for setting up offices in any form with this nodal agency. Coming to the instant case, it is established that PATH by carrying out the clinical trials for HPV vaccines in Andhra Pradesh and Gujarat under the pretext of observation/demonstration project has violated all laws and regulations laid down for clinical trials by the Government**.** While doing so, its sole aim has been to promote the commercial interests of HPV vaccine manufacturers who would have reaped windfall profits had PATH been successful in getting the HPV vaccine included in the UIP of the Country. This is a serious breach of trust by any entity as the project involved life and safety of girl children and adolescents who were mostly unaware of the implications of vaccination. The violation is also a serious breach of medical ethics. This act of PATH is a clear cut violation of the human rights of these girl children and adolescents. It also deems it an established case of child abuse. The Committee, therefore, recommends action by the Government against PATH. The Committee also desires that the National Human Rights Commission and National Commission for Protection of Children Rights may take up this matter from the point of view of the violation of human rights and child abuse. The National Commission for Women should also suo motu take cognizance of this case as all the poor and hapless subjects are females. The Ministry of Health and Family Welfare should without wasting time report the violations indulged in by PATH to international bodies like WHO and UNICEF so as to ensure that appropriate remedial action is initiated by these agencies worldwide.

The Committee also desires that the Ministry of Health and Family Welfare may take up the matter through the Ministry of External Affairs with the US Government so as to ensure that appropriate action is taken against PATH under the laws of its Country of origin in case of any violations of laws there.

Prof Ranjit Roy Chaudhury Committee Report

31. With such a stinging indictment of the government, the best that the government could do was to set up a Committee with Prof. Ranjit Roy Chaudhury as its Chairman. In view of the 59th Report which specifically recommended that "all experts must be made to file the conflict of interest declaration outlining all past and present pecuniary relationships with entities that may benefit from the recommendations given by such experts", the Chairman himself ought to have filed a conflict of interest declaration. He did not do so. This default was deliberate and serious and the government acted malafide in appointing him. It turns out that he is the Chairman of the Research Task Force of the Apollo Hospitals Educational and Research Foundation (AHERF) which is the largest body conducting clinical trials in India and currently conducting a minimum of 200 trials. Its website promises a one stop window service for multinationals. In view of the observations in the 59th Report should the government have appointed such a person on such an important Committee.

32. This is especially so since the Chairman steers the Committee in the direction of making India the guinea pig testing centre of the world in the following terms:

> "In today's era of globalization, the availability of India's able and skilled medical fraternity, the many world-class medical institutions and the large treatment naïve population have put this country in the enviable position of being a potential global hub for clinical research. Also, cost competitiveness and technological infrastructure have given Indian industries and research institutions a definite advantage over other countries in contributing to global drug development in a significant way. In this new environment, many multinational corporations (MNCs) have been attracted to participate in clinical trials in this country."

33. If Phase IV trials which are least dangerous have been conducted in India in such an irregular and unprofessional manner, the question is to be asked whether Recommendation 17 is justified at all. This is as under:

> "All NCEs/NMEs undergoing clinical trials anywhere can also undergo parallel Phase II and Phase III trials in India after carrying a safety assessment through Phase I trials."

34. This is the main recommendation indicating the hand of the pharmaceutical companies and particularly multinational companies in the making of this report. In these few lines India opens up and becomes the guinea pig testing centre of the world for multinationals who will conduct trials in India at 20% of the cost abroad and within a regulatory system that is lax and corrupt. The trick lies in the words "undergoing clinical trials anywhere". Therefore, if a studious clinical trial is going in some remote under developed country that gives corporations the right to conduct Phase I and Phase II trials in India. Secondly, DGCI has no mechanism for determining whether a trial is going on abroad and acts on the basis of approvals for clinical trials abroad. Thus, all that the corporation has to do is to get an approval from a regulator abroad and then, without commencing a clinical trial, produce that approval before the DCGI to get approval for a parallel trial in India and thereafter start the trial self. All these trials in India are basically for patented products of multinationals which the MNC seeks to convert into a useable drug. There is no benefit for the nation.

35. The current legal requirement for concurrent Phase II and Phase III trials in India is as under:

> " for new drug substances discovered in countries other than India, Phase I data as required under items 1, 2, 3, 4, 5 (data from other countries) and 9 of Appendix I should be submitted along with the application. After

submission of Phase I data generated outside India to the Licensing Authority, permission may be granted to repeat Phase I trials and/or to conduct Phase II trials and subsequently Phase III trials concurrently with other global trials for that drug. Phase III trials are required to be conducted in India before permission to market the drug in India is granted "

36. The 162 NCE/NMEs approved by the DCGI have supposedly passed through the animal/laboratory stage and are now to be tested on Indian citizens. In some of these drugs even the animal/laboratory data is suspect. For example, the pfizer drug zonipuride was cleared by the DCGI and the Ethics Committees even though the animal testing period was only for one month and not the mandated 3 months.

37. The recommendations to allow trials in India of NCEs/NMEs is contrary to Rule 30 B of the Drugs and Cosmetic Rules, 1945 which is as under:

> "Prohibition of import of certain drugs.- No drug, the manufacture, sale or distribution of which is prohibited in the country of origin, shall be imported under the same name or under any other name except for the purpose of examination, test or analysis."

38. Recommendation 18(a) is as under:

> "Drugs which have already been on the market in well-regulated countries with good post-marketing surveillance (PMS) for more than four years and which have a satisfactory report may be granted marketing licence, subject to strict PMS for four to six years. The period of four years may be reduced or waived off in cases where no therapy or only palliative therapy is available, or in national healthcare emergencies."

39. Thus the Committee is doing away with all trials in India for drugs from developed countries which have been in use for four years notwithstanding the fact that most of the drugs banned in India and abroad are based on adverse effects invariably recorded after four years and sometimes even upto 10 years. No developed country would allow a drug developed in India and marketed for four years to be allowed to be marketed in any developed country merely on this basis. Moreover, the rationale for Phase III trial is to check the effect of the drug which has been approved for populations of the developed countries, on ethnically diverse populations as found in India and the developing world.

40. Recommendation 5 is as under:

> "The 12 drug advisory committees which are functioning at present will be replaced by one broad expertise-based Technical Review Committee to ensure speedy clearance of applications without compromising on quality of data and rules and

regulations. The Committee would be assisted as required by appropriate subject experts selected from the Roster of Experts.

41. Pursuant to the 59th Report, government of India set up 12 new Drug Advisory Committees, each with about 12 highly qualified and reputed doctors, pharmacologists and other experts. All from government medical colleges to ensure that the experts are genuinely persons of independence who can give expert testimony in the public interest. This was done pursuant to the observation in the 59th Report which is as under:

> "7.35. The Committee is of the view that many actions by experts listed above are clearly unethical and may in violation of the Code of Ethics of the Medical Council of India applicable to doctors.
>
> 7.36. There is sufficient evidence on record to include that there is collusive nexus between drug manufacturers, some functionaries of CDSCO and some medical experts."

42. After the government set up these excellent subject-wise New Drug Advisory Committees, there was disquiet in the industry and accordingly the Committee disbanded all the 12 Advisory Committees abovementioned.

43. The Committee use of the word "new drug" is done in a restricted way as under:

"122-E: Definition of new drug.- For the purpose of this part, new drug shall mean and include.- (a) A drug, as defined in the Act including bulk drug substance which has not been used in the country to any significant extent under the conditions prescribed, recommended or suggested in the labeling thereof and has not been recognized as effective and safe by the licensing authority mentioned under Rule 21 for the proposed claims.

Provided that the limited use, if any, has been with the permission of the licensing authority.

(b) A new drug already approved by the Licensing Authority mentioned in Rule 21 for certain claims, which is now proposed to be marketed with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration.

A fixed dose combination of two or more drugs, individually approved earlier for certain claims, which are now proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in an already marketed combination is proposed to be changed, with certain claims, viz. indications, dosage, dosage form (including sustained release dosage form) and route of administration. (See items (b) and (c) of Appendix

VI to Schedule Y.)

Explanation.- For the purpose of this rule.-

(i) All vaccines shall be new drugs unless certified otherwise by the Licensing Authority under Rule 21;

(ii) A new drug shall continue to be considered as new drug for a period of four years from the date of its first approval or its inclusion in the Indian Pharmacopoeia, whichever is earlier

44. This is contrary to 122 E of the Drugs and Cosmetic Rules 1945 which includes new indications, dosages, dosage forms (for example sustain release), new ratio of ingredients in already marketed FDCs etc. Thus the Committee seeks to restrict the need for clinical trials contrary to the rules.

45. On Ethics Committees, the Committee makes the following observations:

"An Institute Ethics Committee (IEC) is formed by an institution or a hospital for the purpose of reviewing research conducted at the institution."

46. It is necessary to understand the pernicious intent and impact of this recommendation in the context of Ethics Committees throughout the country putting their rubber stamp on illegal trials. The hospital or institution doing the trial conveniently sets up an

Ethics Committee consisting of doctors who are the friends and associates (in the Indore trials even the relatives) of the doctors performing the trials. Their roles are interchangeable and they help each other as the doctor doing a particular trial would later be on the Ethics Committee of another trial conducted by doctors who were on an earlier Ethics Committee. There is therefore, an inbuilt tendency to clear all trials and to ignore illegalities.

47. Secondly, doctors in private hospitals are not full time employees and are invariably appointed as consultants who could be hired and fired. Thus it is not possible for a doctor in a private hospital on an Ethics Committee to protest in respect of an unethical act.

48. Thirdly, there is **no mechanism in place to make non recording of deaths/SAEs a punishable offence**.

49. This is the reason why petitioner seeks the following directions from this Court:

a) For an order directing the government not to permit any clinical trial in a private establishment with a further direction to government to only allow clinical trials in government medical colleges done by experts on the subject.

50. On page 19 of the Report, the Committee makes a subtle but important twist with regard to concurrent trials. The Parliamentary

Committee report referred to developed countries as including the EU. This phrase is as under.

> "Countries with efficient and good regulatory agencies such as the USA, UK, countries of the European Union, Japan, Australia, Canada, etc. should be marketing the drug under study."

51. With these twist clinical trials carried out in countries such as Estonia and Turkey with poor regulatory regimes could be taken into consideration in India for conducting parallel trials. The EU has a two tier regulatory system for approvals. The first are the national approvals based on approvals granted by the National Drug Regulator and these approvals are valid only for the country concerned and are not valid for other EU countries. The second is the community-wide approvals. Thus, though the current legal regime in India recognizes only the community-wide approvals, the Committee appears to make a sly shift to the limited national approvals of an EU country.

52. At page 23 of the report another strange clause is found.

> "Waiver of clinical trials: provision of a waiver should be used only when alternative mechanisms for ensuring protection of the rights and welfare of human subjects are acceptable and are in place."

53. The Report speaks extensively of Accredited Ethics Committees in Chapters 5, 6 and 7, however, there is not a word about members of the Ethics Committees being required to make a written declaration on conflict of interest. On the contrary, the Institutional Ethics Committees are formed by the head of the institute itself.

54. Informed consent is referred to at page 77 of the report or elsewhere and is one of the most vexed issues in clinical trials as trials done in India have proven to be done on indigenous, malnourished, illiterate and poverty stricken sections of the population without even a pretence of informed consent. With the startling cases coming to court one would have thought that this Committee would have given much emphasis on punishment for violation of the informed consent requirement. In developed countries criminal prosecutions follow such violations. All that the Committee has to say is as under:

> "Any violation of the informed consent process will be dealt with as a serious lapse on the part of the investigations, for which the PI can be blacklisted or debarred from clinical trials for a period of up to five years.

55. In respect of compensation it is stated in report as under:

> "In totally proven unrelated cases, e.g. building collapse, drowning, road accident, etc. occurring to the

patient undergoing a clinical trial, compensation may not be payable."

56. Compensation for Deaths and Serious Adverse Events (SAEs) on account of or during or related to a clinical trial is a grey area and it is also an issue relating to exploitation of the persons undergoing the clinical trial. In many cases it is proved there are large number of persons died or suffered SAEs as a result or during the trial and invariably a defence of the corporation is accepted that most of the deaths were unconnected with or unrelated to the trial. The decision as to the relation between the death/SAE and the trial is made by the corporation itself and no independent verification is required. This is why excuses such as snake bites, falling into a well and the like are accepted as showing no link between the trial and the death. Even otherwise medical opinion would be seriously divided over whether a death/SAE is the result of a trial with most independent experts holding that the majority of deaths/SAEs were related to the trial and all the doctors associated with the trial holding the opposite. A salutary rule would be to handsomely cover all persons undergoing clinical trial for deaths/SAEs and also adverse events whatever be the relation with the trial. This medical coverage would also cover deaths/SAEs after the trial is over for a specific period since many of the events occur after the trial.

57. The non application of mind on this issue is palpable in the use of the above quoted phrase. A hospital building in which the

clinical trial is conducted may collapse. Would be patient/relatives not be entitled for compensation on account of injury or death due to a building collapse. Many drugs administered during a trial caused disorientation and seizures. A person in a village may fall into a well or a person swimming in a lake may get dizziness and drown. Would they be not entitled to compensation. A patient may be traveling to or from the hospital where the trial is being conducted. Should there be a motor accident would compensation not be payable. In the AMRI Hospital, Kolkata fire, clinical trial patients died. Are they not to be paid compensation merely because they died not on account of the trial but due to the fire?

58. The pro corporate tilt is also visible from recommendation (g) where a sponsor may appeal the decision of the IEC but not the patient. This clause is as under:

> "If the sponsor or his representative/investigator is aggrieved by the decision of the IEC on the causality, he will have the right to seek a review of the decision within 14 days of the receipt of the recommendation of the IEC by the sponsor/investigator."

59. Recommendation (m) is likewise sharply titled against the patient.

> "The committee deliberated on the very important issue as to whether patients suffering from terminal illnesses/cancer should be entitled to compensation in

the event of any SAE related to the clinical trial. The Committee is of the opinion that in the cases of clinical trials being carried out on patients suffering from terminal illness such as cancer, compensation may be not given if the primary end-point is death, but may be payable if the IEC after deliberation is of the considered opinion that

- there is increase in the SAEs occurring in such a patient compared to a standard treatment and which may be irreversible or

- life expectancy has been severely curtailed."

60. Cancer is no longer incurable. It may or may not result in death. This recommendation puts the onus on the patient to establish what could be a fact very difficult to prove.

G.S.R. 53(E), GSR 63(E), GSR 72 (E)

61. I now make a critique of the notifications dated 30.1.03 [G.S.R. 53(E)], 1.2.13 [GSR 63(E)] and 8.2.13 [GSR 72 (E)] issued by the Union of India during the progress of this case.

62. Notification GSR 53 (E) is included as Appendix 12 to Schedule Y of the Drugs and Cosmetics Rules, 1945 and deals with "compensation in case of injury or death during criminal trials." Clause 5 is, inter alia, as under:

"The sponsor or its representative, **<u>whoever had obtained permission from the licencing authority</u>** for conduct of the criminal trial, shall provide financial compensation…"

63. The corporation behind the clinical trial rarely gets directly associated with the trial but follows the modus operandi of engaging contract research organizations (CROs) for conducting the trial. Agreements are entered into between the pharmaceutical companies and the CRO requiring very high standards knowing full well that these standards will not and are not being met. Often, it is the CRO that obtains permission from the licencing authority to do the clinical trial. When deaths and serious adverse events occur the pharmaceutical companies invariably take the defence that the CRO is at fault and only the CRO can be sued. These CROs do not generally have adequate financial resources to pay compensation and it is quite possible that if they are faced with a substantial claim, that they will claim to be insolvent. Therefore, these rules are framed by the central government on the prompting of the pharmaceutical companies so as to insulate the companies from liability to pay compensation and to shift the liability onto the CRO.

64. Clause 6 is also introduced on the prompting of the MNCs. It is the investigator (CRO) which is required to report all serious and unexpected adverse events. The investigator is precisely the person interested in avoiding collecting data on deaths/SAEs and if information comes to his notice he would go out of his way to

suppress such data. In this regard petitioner refers later to the 72nd Parliamentary Committee Report on the Role of CROs (Investigators) in clinical trials. Clause 6(a) is as under:

> "6(a) the **investigator** shall report all serious and unexpected adverse events to the licencing authority…"

65. I now deal with the notification GSR 63(E) dated 1.2.13. The relevant part is as under:

> "clause 3 " if any sponser including their employees, subsidiaries and branches , their agents, contractors and sub-contractors, investigators conducting clinical trial and clinical trial sites fail to comply with any of the above conditions, the licensing authority, may, after giving an opportunity to show cause why such an order should not be passed by an order in writing stating the reasons thereof:-
>
> a) Issue warning letter giving details of deficiency found during the inspection which might affect the right or well-being of the clinical trial subject or the validity of the study conducted at that site;
>
> b) Recommend that study may be rejected or discontinued;
>
> c) Suspend or cancel the clinical trial permission;

d) Debar the investigator(s). sponsor including their employees, subsidiaries and branches, their agents, contractors and sub-contractors to conduct any clinical trial in future."

66. From the above it can be seen that if the clinical trial is done contrary to the conditions imposed by the licencing authority and even if the trial results in deaths /SAEs there is no punishment stipulated under the Rules.

67. I now deal with GSR 72(E) dated 8.2.13 dealing with registration of Ethics Committees. This appears to be only a formality since any qualified doctor or group of doctors can obtain registration on making a simple application providing certain data. This notification introduces a new rule 122 DD. Clause 3(2) and 3(3) lays down the composition of the Ethics Committee and information required to be submitted by the applicant for registration of Ethics Committees. A perusal of this clause will show that the main problem namely that the private hospitals doing the clinical trials are appointing the Ethics Committees, has not been dealt with. The private hospitals are committed to turn India into a global centre for cheap clinical trials. Their motive is commercial. They have hardly a care for the protection of the rights of the poor persons on whom test will be conducted. They appoint the members of the Ethics Committees. Members of these Ethics Committees are consultant doctors in their hospitals. They could be fired at a moment's notice. Thus, there is an inherent conflict of

interest in allowing private bodies to be involved in clinical trials in the first place.

CONCLUSION

68. The reasons why clinical trials ought to be restricted and seriously supervised is because there is an overwhelming need to protect the citizens of India especially the poor and illiterate against the unscrupulous.

69. The second reason is that the benefits of these trials largely accrue to the multinational corporations who use these trials to convert a patented chemical into a usable drug. All that India gets in terms of contracts to do these trials are equivalent to "crumbs off the table".

70. Instead of India getting involved in a rat race with China (while India was preferred destination for foreign multinational companies sometime back, China is now fast taking over) business of carrying out tests on human beings, it is far far better that the DCGI in India concentrate on (i) the removal of bad drugs, (ii) banning all drugs that are banned globally in developed countries (iii) not allow any fixed dose combination if such a combination is not permitted in a developed country.